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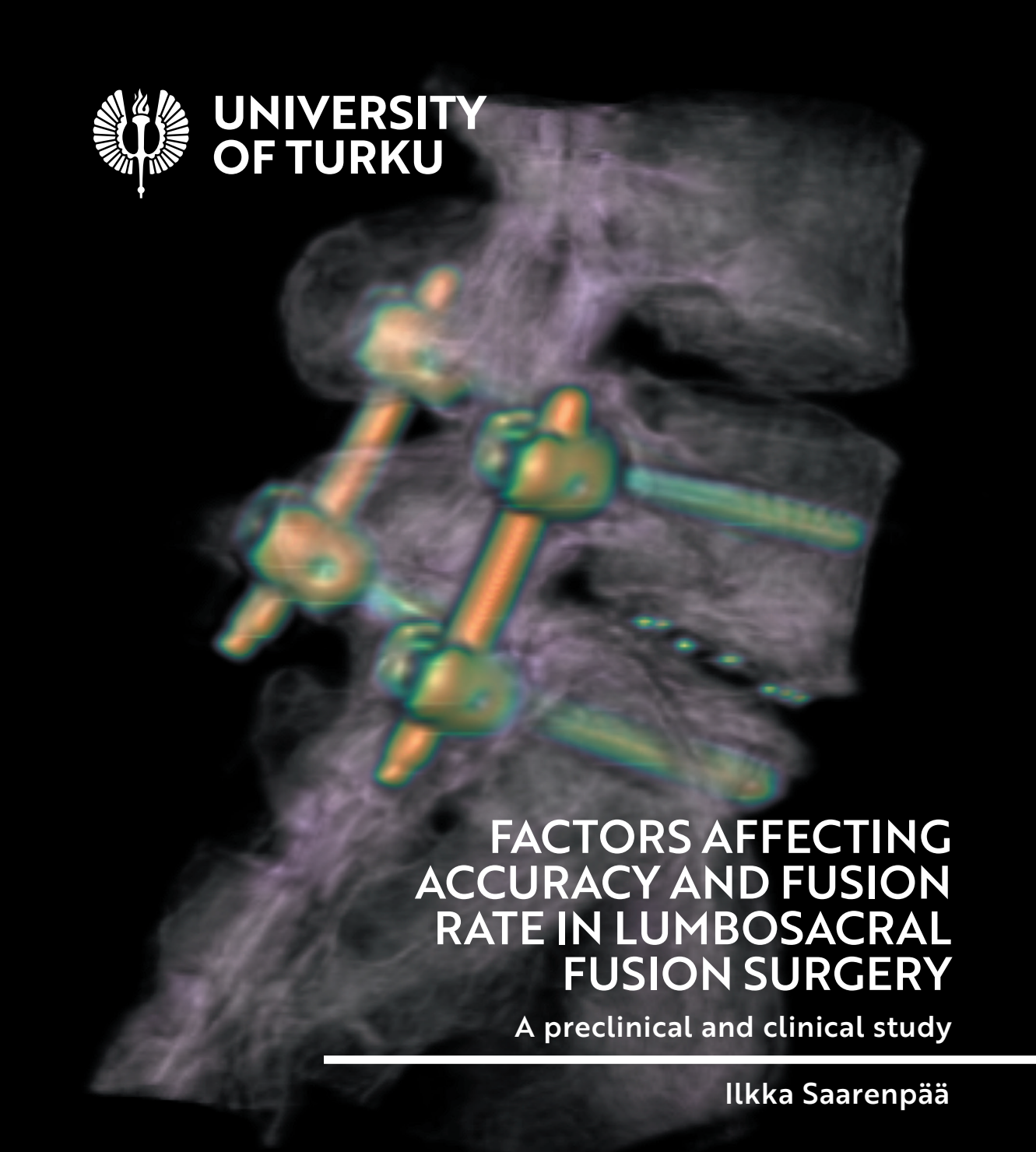

# FACTORS AFFECTING ACCURACY AND FUSION RATE IN LUMBOSACRAL FUSION SURGERY

## A preclinical and clinical study

Ilkka Saarenpää

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA - SER. D OSA - TOM. 1388 | MEDICA – ODONTOLOGICA | TURKU 2018

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To my family

# ABSTRACT

Ilkka Saarenpää
Factors Affecting Accuracy and Fusion Rate in Lumbosacral Fusion Surgery

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Annales Universitas Turkuensis, Medica-Odontologica, Turku, Finland, 2018

Lumbosacral fusion surgery is indicated in symptomatic degenerative lumbosacral disorder, when the origin of pain is demonstrated to lie within the restricted number of functional spinal units and when the pain is refractory to the conservative treatment, to eliminate painful motion of the spinal units. Inaccurate placement of pedicle screws may cause neurological symptoms, and result in early hardware failure and return of spinal instability symptoms. All spinal instrumentation eventually fails without solid bony fusion, and the presence of symptomatic bony non-union at least a year after fusion surgery is defined as pseudoarthrosis. Bioactive glasses (BAGs) are synthetic, biocompatible, osteoconductive and osteostimulative materials with angiogenic and antibacterial properties, able to bond to bone.

In a study of 147 patients and 837 pedicle screws placed due to degenerative lumbosacral spine disorder, 14.3 % breached the pedicle. New neurological symptoms corresponding to the breach were observed in 25.9 % of patients with pedicle breach, and 89.2 % of the symptomatic breaches were either medially or inferiorly. A preclinical controlled study of novel BAG S53P4 putty showed good biocompatibility, slightly higher intramedullary ossification of putty group compared to the control group, and that the binder agent did not disturb formation of new bone in vivo. The interbody fusion rate was 95.8 % with BAG S53P4 putty as bone graft expander with autograft in clinical lumbosacral interbody fusion, indicating at least as good interbody fusion results as the presently used materials. One early operative subsidence remaining unchanged over the study period was observed with putty.

Keywords: bioactive glass, bone graft expander, pedicle screw, lumbar spinal fusion

# TIIVISTELMÄ

Ilkka Saarenpää
Lannerangan luudutusleikkausten tarkkuuteen ja luutumiseen vaikuttavat tekijät

Turun yliopisto, Lääketieteellinen tiedekunta, Kliininen laitos, Neurologia, Neurokirurgia; Turun kliininen tohtoriohjelma

Annales Universitas Turkuensis, Medica-Odontologica, Turku, Finland, 2018

Lannerangan luudutusleikkaus voidaan tehdä oireisessa lannerangan rappeumasairaudessa, kun kivun syyn on osoitettu sijaitsevan rajallisessa määrässä selkärangan toiminnallisia yksikköjä ja kun kipu ei vähene leikkauksettomilla hoidoilla. Leikkauksella voidaan poistaa kipua tuottava selkärangan toiminnallisten yksikköjen liike. Epätarkka pedikkeliruuvien asettaminen voi aiheuttaa neurologisia oireita ja johtaa nopeaan kiinnitysosien irtoamiseen ja rangan epätukevuusoireiden palaamiseen. Suuri osa selkärangan kiinnityslaitteista irtoaa lopulta, jollei luutumista kiinnitettyjen kohtien välillä tapahdu. Vuoden kuluttua luudutusleikkauksesta oireista luutumatonta kiinnityskohtaa nimitetään pseudoartroosiksi. Bioaktiiviset lasit ovat synteettisiä, bioyhteensopivia, osteokonduktiivisia ja osteostimulatiivisia materiaaleja, joilla on angiogeenisiä ja antibakteerisia ominaisuuksia, ja ne voivat sitoutua suoraan luuhun.

147 potilaalle lannerangan rappeumasairauden vuoksi asetetut 837 pedikkeliruuvia käsittävän tutkimuksen mukaan 14.3 % ruuveista rikkoi luisen pedikkelin seinämän. 25.9 %:lla potilaista, joilla ruuvi läpäisi pedikkelin seinämän, ilmeni uusia neurologisia oireita, ja 89.2 %:lla oireisista potilaista pedikkeliruuvi läpäisi pedikkelin seinämän mediaalisesti tai inferiorisesti. Prekliinisessä kontrolloidussa tutkimuksessa uudenlainen bioaktiivisesta lasista valmistettu S53P4 luunkorviketahna todettiin bioyhteensopivaksi, ja sen avulla saavutettiin hieman vertailuryhmää parempi luutuminen luuydinontelossa. Tahnan sidosaineen ei eläinkokeessa todettu häiritsevän luun muodostumista. Kliinisessä tutkimuksessa saavutettiin 95.8 %:n luutuminen käytettäessä S53P4 biolasitahnaa yhdessä oman luun kanssa lannerangan nikamasolmujen välisessä luudutuksessa. Siten yhdessä oman luun kanssa käytettäessä S53P4 biolasitahnalla saadaan aikaan vähintään yhtä hyvä nikamasolmujen välinen luutuminen kuin nykyisin käytettävillä synteettisillä luunkorvikkeilla. Tutkimuksessa todettiin yksi leikkauksen yhteydessä tapahtunut nikamasolmujen välisen implantin päätelevyyn painuminen, jonka suuruus ei muuttunut seurantakuvantamisissa.

Avainsanat: bioaktiivinen lasi, luunkorvike, pedikkeliruuvi, lannerangan luudutus

## TABLE OF CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| μCT | High-resolution micro-computed tomography |
| ACS | Absorbable collagen sponge |
| ALIF | Anterior lumbar interbody fusion |
| AP | Anterior-posterior |
| BAG | Bioactive glass |
| bFGF | Basic fibroblast growth factor |
| BMA | Bone marrow aspirate |
| BMP | Bone morphogenic protein |
| BSF | Brantigan-Steffee-Fraser |
| CAS | Computer-assisted surgery |
| CCD | Charge-coupled device |
| CFR | Carbon-fiber-reinforced |
| CI | Confidence interval |
| CoCr | Cobalt chromium |
| CSD | Critical size defect |
| CSF | Cerebrospinal fluid |
| CT | Computed tomography |
| DBM | Demineralized bone matrix |
| EDXA | Energy-dispersive X-ray analyser |
| EZ | Elastic zone |
| FDA | US Food and Drug Administration |
| FSU | Functional spinal unit |
| FTIR | Fourier transform infrared spectroscopy |
| GRS | Graphic rating scale |
| HA | Hydroxyapatite |
| HCA | Hydroxycarbonate apatite |
| HIF | Hypoxia-inducible factor |
| HRQOL | Health-related quality of life |
| ICF | International classification of functioning, disability and health |
| ICP | Inductive coupled plasma |
| IR | Infrared |
| MI | Minimally invasive |
| MIS | Minimally invasive surgery |
| MISS | Minimally invasive spine surgery |

| | |
|---|---|
| MMA | Methyl methacrylate |
| MOS | Medical outcome study |
| MSC | Mesenchymal stem cell |
| NCSP | Nordic classification of surgical procedures |
| NRS | Numerical rating scale |
| NZ | Neutral zone |
| ODI | Oswestry disability index |
| OP | Osteogenic protein |
| PCR | Polymerase chain reaction |
| PEEK | Polyetheretherketone |
| PEG | Polyethylene glycol |
| PLF | Posterolateral fusion |
| PLGA | Polylactic-co-glycolic acid |
| PLIF | Posterior lumbar interbody fusion |
| rh | Recombinant human |
| RMDQ | Roland-Morris disability questionnaire |
| ROM | Range of motion |
| SBF | Simulated body fluid |
| SD | Standard deviation |
| SEM | Scanning electron microscopy |
| TCP | Tricalcium phosphate |
| TGF | Transforming growth factor |
| TLICS | Thoracolumbar injury classification and severity score |
| TLIF | Transforaminal lumbar interbody fusion |
| TOF | Time of flight |
| VAS | Visual analogue scale |
| VEGF | Vascular endothelial growth factor |
| VRS | Verbal rating scale |
| WHO | World Health Organization |
| WHOQOL | World Health Organization’s quality of life questionnaire |
| XLIF | Extreme lateral lumbar interbody fusion |
| XRD | X-ray diffraction |

# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications referred to in the text by their Roman numerals (I-III).

I Saarenpää I, Laine T, Hirvonen J, Hurme S, Kotilainen E, Rinne J, Korhonen K, Frantzén J. Accuracy of 837 pedicle screw positions in degenerative lumbar spine with conventional open surgery evaluated by computed tomography. Acta Neurochirurgica 2017; 159:2011-2017. DOI: 10.1007/s00701-017-3289-7.

II Saarenpää I, Stoor P, Frantzén J. BAG S53P4 putty as bone graft substitute - a rabbit model. Biomedical Glasses 2017; 3:30-40.

III Saarenpää I, Hirvonen J, Rinne J, Frantzén J. Bioactive glass putty (S53P4) as bone graft expander in minimally invasive lumbosacral interbody fusion. Accepted for publication in Journal of Minimally Invasive Spine Surgery & Technique (JMISST).

# 1 INTRODUCTION

According to a recent study, years lived with disability caused by low back pain increased by 54 % globally between the years 1990 and 2015 (Hartvigsen et al. 2018). Primarily, the treatment of low back pain includes education and resumption of normal activities, and psychological programmes for those with persistent symptoms (Foster et al. 2018). Lumbosacral fusion surgery is indicated in unstable lumbar fractures; in idiopathic or degenerative deformities according to certain criteria; in bone tumours and spinal infections due to primary or postoperative instability or progressive deformity; and in symptomatic degenerative disease, when the origin of pain is proved to lie within the limited number of functional spinal units, and when the pain is refractory to the conservative treatment (physical therapy and other non-operative measures), to eliminate painful motion of the spinal units (Allen et al. 2009, Phillips et al. 2013).

Lumbosacral fusion can be achieved by posterolateral fusion, by different approaches of interbody fusion or by both of them together, and minimally invasive approaches seem to reduce the approach-related morbidity (Foley et al. 2003). Based on biomechanical conditions, posterolateral fusion is more difficult to achieve than interbody fusion, but subsidence, i.e. sinking of an interbody implant into adjacent vertebral endplate, may defeat the purpose of the interbody fusion (Vaidya et al. 2008, Abdu et al. 2009, Tokuhashi et al. 2009). In the placement of pedicle screws in either of the fusion techniques, a breach of pedicle by the screw may cause new neurological symptoms, and result in a loss of screw pullout strength leading to a risk for early hardware failure and return of spinal instability symptoms (Gelalis et al. 2012, Costa et al. 2013). Generally, the accuracy of pedicle screw placement can be improved by adopting different navigation methods including intraoperative imaging instead of the freehand technique assisted by radiographs (Laine et al. 2000, Mason et al. 2014).

Since all spinal instrumentation eventually fails without solid bony fusion, bone grafting is of vital importance for successful fusion (Kalfas 2001). Autograft is still considered the gold standard graft material for spinal fusion, because it is the only graft material presenting a natural combination of osteogenic, osteoinductive and osteoconductive properties promoting bone formation and fusion (Fischgrund et al. 1997). However, autograft harvesting is associated with limited local availability, donor-site morbidity, increased operating time and blood loss (Khan et al. 2005). Allografts avoid the drawbacks of autografts but have several disadvantages regarding processing, and, together with demineralized bone matrix, carry a risk of disease transmission (Grabowski et al. 2013). Bone morpho-

genic protein 2 (BMP-2) is a bone graft enhancer, which increases fusion rates but does not provide any structural support and is associated with several complications including subsidence in interbody fusion applications (Carragee et al. 2011). Synthetic ceramics, tricalcium phosphate (TCP) and hydroxyapatite (HA), have not shown excellent performance as bone graft expanders in several earlier studies (Hsu et al. 2005, Korovessis et al. 2005, Kong et al. 2013, Thaler et al. 2013).

Bioactive glasses (BAGs) are synthetic, biocompatible, osteoconductive and osteostimulative materials with angiogenic and antibacterial properties, and are able to interfacially bond to bone (Hench 2006, Jones 2013). The key phenomenon in the functioning of BAGs, with main components of $SiO_2$, $Na_2O$, CaO and $P_2O_5$ in the narrow range, is controlled rates of release of critical concentrations of soluble silica and calcium ions leading to up-regulation and activation of genes in osteoprogenitor cells (Hench 2009). The BAGs have been previously used as bone graft expanders in instrumented spinal fusion surgery with success in a few studies (Ilharreborde et al. 2008, Frantzén et al. 2011, Rantakokko et al. 2012).

We set out to study the common technical factors affecting the outcome of lumbosacral fusion surgery from the point of view of the practising spine surgeon: accurate and tight placement of pedicle scews, and factors that affect the fusion rate. Our first objective was to assess the pedicle screw placement accuracy of a very experienced neurosurgeon using the freehand technique assisted by radiographs, based on comprehensive data. We also aimed to evaluate preclinically the biocompatibility and bone regeneration performance of a novel BAG S53P4 putty in vivo. In addition, we investigated clinically the interbody fusion rate acquired with the mixture of BAG S53P4 putty and autograft, and the subsidence of the intervertebral cage in minimally invasive lumbosacral interbody fusion surgery.

# 2 REVIEW OF THE LITERATURE

## 2.1 Lumbar spinal fusion

### *2.1.1 Background*

Spinal fusion surgery was first introduced to treat spinal fractures. The early era began when the American surgeon William F. Wilkins successfully performed the first internal fixation of the spine in 1887. He reduced and fixed a dislocated Th12/L1 vertebrae fracture of a new-born infant by a figure of eight carbonized silk wire passed around the pedicles of Th12 and L1 vertebrae (Hadra 1975, Gruber et al. 2008). In December of 1890, the surgeon, Berthold E. Hadra, fastened together an unstable dislocated C6/C7 fracture with silver-wire loops in a figure of eight placed around the spinous processes of the C6 and C7 in Austin, Texas (Hadra 1975). The patient had fallen down to the floor almost twelve months before the operation, but his myelopathy symptoms fairly well resolved three months after the operation (Hadra 1975).

The German orthopaedic surgeon, Fritz Lange, began treating spondylitic spine with internal splints of steel wire on both sides of the spinal processes fastened with silver wire to the spinal processes in 1902 (Lange 1986). Later, he switched to use tin-coated rods fastened with paraffin-sublimate silk. Two American orthopaedic surgeons, Russell A. Hibbs and Fred H. Albee, developed independently the technique of non-instrumented osseous fusion to stabilize the deformed tuberculous spondylitic spine in New York at about the same time (Hibbs 1964, Albee 2007). In December of 1910, Hibbs carried out his first operation where spinous processes were divided at their base and placed longitudinally in the interspinous space touching with either end the base from which the processes were removed (Hibbs 1964). This is considered to be the first posterior spinal fusion operation using autologous bone graft. In June 1911, Albee started his series where he sagittally split the spinous processes into equal halves and placed an autologous tibia strip between them (Albee 2007).

The fusion era for the treatment of degenerative lumbar diseases began in 1932, when the orthopaedic surgeon Norman Capener first described the anterior lumbar interbody fusion (ALIF) procedure to treat spondylolisthesis in Exeter, the UK (Capener 1932). The posterior lumbar interbody fusion (PLIF) technique was introduced in 1944 by the American orthopaedic surgeons, Henry Briggs and

Paul R. Milligan (Briggs et al. 1944). They used bone chips from laminectomy in the intervertebral space as interbody bone grafts. Further, the American orthopaedic surgeon Irwin A. Jaslow placed the removed part of spinous processes into the intervertebral space (Jaslow 1946). In 1952, the American neurosurgeon Ralph B. Cloward described his technique, which used allogeneic bone grafts from bone banks in PLIF from 1946 (Cloward 1952). Later, in 1953, he published successful results of his case series of 321 operations using both autologous iliac crest bone graft and allogeneic bone grafts in PLIF (Cloward 1953).

In spite of modified fusion methods and improved operative technique, pseudoarthrosis, particularly in the lumbosacral region, still remained a problem. This led to an investigation of the posterolateral region of the spine as a possible area for fusion. The technique and the initial results of posterolateral lumbar and lumbosacral fusion were described first by the American orthopaedic surgeon Melvin B. Watkins (Watkins 1953). It consisted of a decortication of the facet joints, the pars interarticularis and the base of the transverse processes, and application and possible securing of corticocancellous iliac crest bone graft block (Watkins 1953). This technique described by Watkins was further modified in order to prevent bone graft block dislocation by using multiple thin iliac strips as graft material by the orthopaedic surgeons, George Truchly and Walter A. L. Thompson (Truchly et al. 1962).

The use of spinal instrumentation originated from the need to provide for ossification leading to spinal fusion without external fixation in order to avoid pseudoarthrosis. The American orthopaedic surgeon Donald E. King began placing vitallium screws through the lateral articulations of facet joints already in 1942 (King 1944). The transpedicular approach to the vertebral body was first presented by Michele and Kueger (Michele et al. 1949). In 1959, Boucher published the technique of lumbosacral fusion using long transpedicular screws (Boucher 1959). This technique was combined with the placement of posterolateral bone graft in 1961 (Pennal et al. 1964). Simultaneously with the evolution of screw fixation methods, the American orthopaedic surgeon, Paul R. Harrington, developed a spinal instrumentation system with multiple modifications consisting of stainless steel rods and hooks for the treatment of scoliosis (Harrington 1962). Additionally, it was applied for the treatment of spine fractures, high-grade spondylolisthesis and other degenerative conditions (Harrington 1973).

The French orthopaedic surgeon, Raymond Roy-Camille, combined earlier efforts with his associates by starting to use pedicle screws with posterior plates to stabilize the lumbar spine for various conditions since 1963 (Roy-Camille et al. 1976, Roy-Camille et al. 1986). A new era in spinal instrumenta-

tion was initiated, when the Austrian-Swiss surgeon Friedrich P. Magerl developed and adopted in clinical use an external spine fixation system with pedicle screws and rods in 1977 (Magerl 1984). Compared to other fixation methods, this system enabled reduction in addition to stabilization, a decrease in the number of vertebrae immobilized and an angle-stable fixation. The disadvantages in the external system gave rise to an internal spine fixation system that further caused the establishment of a new universal segmental instrumentation with rods, laminar and pedicular hooks, pedicle screws, and a device for transverse traction in general use (Dick et al. 1985, Aebi et al. 1988, Cotrel et al. 1988). In the 1980's, the American orthopaedic surgeon George W. Bagby introduced his concept of a hollow interbody cage filled with bone graft to provide a strong structural support and enhance fusion for human use (Bagby 1988, Kuslich et al. 1998). Further, the polyaxial screw heads have been used to facilitate the rod-screw connection in the pedicle screw instrumentation systems since the late 1990's.

### *2.1.2 Spine biomechanics*

The functional spinal unit (FSU), or motion segment is the basic element of the spine, consisting of two adjacent vertebrae, the facet joints, the intervertebral disc, and the spinal ligaments (Panjabi et al. 1980). The whole spine should be considered as a structure of multiple FSUs coupled in series, which make its behaviour to consist of independent units.

The vertebrae support the spine for axial compression. Therefore, their strength increases along the spinal column from cervical to lumbar region that manifests in an increasing cross-sectional area (Oxland 2016). In the vertebrae, the transverse and spinous processes are the important attachment points for the ligaments and skeletal muscles, which initiate spine motion and are particularly important for spinal stability (Lumsden et al. 1968). The superior and inferior articular processes of the facet joints set the natural limits for the intersegmental motion in anterior-posterior shear and torsion. If their ability to resist the shear load is weakened, a slip of vertebra with relation to adjacent vertebra may occur. Also, even a minimal loss in the intervertebral disc height has been shown to cause a marked increase in peak contact pressure across the facet joints: a 1 mm loss in disc height led to a 35.9 % increase in peak pressure across the facet joint, and a 4 mm decrease to a 61.4 % increase in peak pressure (Dunlop et al. 1984). This predisposes the facet joints to osteoarthritis.

Axial compression load is further transferred and distributed through the avascular intervertebral disc, which bears a complex combination of axial, bend-

ing and torsional forces. The axial load component is supported by osmotic intrinsic swelling pressure of the inner gelatinous nucleus pulposus, whereas the osmotic swelling is proportional to the concentration of the hydrophilic proteoglycans inside the outer fibrous annulus (Urban et al. 1985). Further, the intrinsic pressure of the nucleus pulposus is resisted by circumferential stresses in the fibrous annulus, which also carries bending and torsional load components (Galante 1967). Compared to external applied axial load per unit of area, pressures within the nucleus pulposus have been measured to be on average 30–50 % higher, and load components in the fibres of anulus at least 3–5 times higher, particularly in the posterior part of the anulus (Nachemson 1960, Nachemson 1963, Galante 1967). In addition to the axial load component, different bending and torsional components, e.g. in tilting backward, have been shown to increase the pressure within the nucleus pulposus and load components in the fibres of anulus even more (Nachemson 1963).

The mechanical response, i.e. the viscoelastic behaviour of the nucleus pulposus has been demonstrated to depend on the load rate: the response is fluid-like flexible at low load rates, but more solid-like stiff at high load rates (Iatridis et al. 1996). With age and degeneration, the nucleus pulposus dehydrates, decreases in size and loses a quantity of proteoglycan aggregates (Pearce et al. 1987). Also, the structure and composition of collagens change, although the total collagen amount remains unchanged (Iatridis et al. 1997). As a result of these alterations, the nucleus pulposus has been shown to behave mechanically more like a solid, also at low load rates (Iatridis et al. 1997). This, together with possible degenerative structural changes in the anulus and endplate, results in a transfer of load components from the nucleus pulposus especially to the posterior part of anulus that may be a cause of structural disruption (Adams et al. 1996).

The spinal ligaments connect adjacent vertebrae along the spinal column. They guide segmental motion of the spine within physiological limits and actively contribute to intrinsic stability of the spinal column by limiting excessive motion at or beyond this range with their mechanoreceptors (Oxland 2016). The ligaments have been shown to stiffen and lose strength with age, and to decrease both stiffness and strength when in parallel with spinal instrumentation (Tkaczuk 1968, Kotani et al. 1998). Together with the erector spinae muscles, the posterior ligamentous complex forms a posterior tension band of the spinal column reacting the axial compression force resting on the anterior column of the spine, likened to the guy wire of the crane. In load displacement testing, removal of the posterior tension band in vitro resulted in a 1.7-fold increase in shear translations, a 2.1-fold increase in bending displacement, and a 2.7-fold increase in torsional rotation (Mcglashen et al. 1987).

Three-dimensional quantification of specimen range of motion, i.e. biomechanical flexibility testing has been used as a general method to measure and quantify the structural properties and motion of the FSU. Flexibility is defined as a structure's ability to deform under the application of load. When the load-displacement performance has been studied in all physiological directions, the bending behaviour of the FSU has been observed to be non-linear in flexion-extension and lateral directions, lumbar axial rotation behaviour to be almost linear and shear behaviour roughly linear or in anterior-posterior direction bi-linear due to facet contact (Panjabi et al. 1994, Frei et al. 2002, Gardner-Morse et al. 2003, Gardner-Morse et al. 2004, Lu et al. 2005, Heuer et al. 2007, Skrzypiec et al. 2012, Schmidt et al. 2013, Oxland 2016). The non-linear behaviour of the FSU led to the definition of the neutral zone (NZ) in addition to the range of motion (ROM), which determines the total extent of motion under a given load. The NZ represents the low stiffness region at small loads due to ligament and intervertebral disc laxity around the neutral position (Oxland 2016). The dislocation beyond the NZ up to the physiological limit is named the elastic zone (EZ) (Panjabi 1992). The extent of the NZ correlates well with the signs of spine instability, and increases as a result of iatrogenic spine injury (e.g. removal of facet), disc degeneration and repetitive loading (Panjabi 1992, Mimura et al. 1994, Gay et al. 2006, Oxland 2016).

Based on the observations of the NZ, clinical spine instability can be defined as a significant decrease in the capacity of the stabilizing system of the spine to maintain the intervertebral NZs within physiological limits so that there is no neurological dysfunction, no major deformity, and no incapacitating pain (Panjabi 1992). In spinal fusion surgery, the spinal instrumentation and the stabilized segment together form a coupled mechanical system that splits loads and mechanical moments. The extent of the NZ decreases with addition of spinal instrumentation and muscle forces (Panjabi et al. 1989, Panjabi 1992).

### *2.1.3 Clinical indications*

Spinal fusion provides stability by fixing the spinal motion segment. Thus, various classification schemes have been developed for determining spinal stability of traumatic thoracolumbar injuries in order to identify the unstable cases that need surgical stabilization (McAfee et al. 1983, Denis 1984, McCormack et al. 1994, Magerl et al. 1994, Vaccaro et al. 2005). The Denis classification system divides the spine into anterior, middle and posterior columns (Denis 1984). Unstable fractures were considered to consist of injures involving at least two col-

umns (Denis 1984). The AO classification system introduced by Magerl divides injury type (A, B, C) by the direction of force applied into compression, distraction and torsion injuries (Magerl et al. 1994). Each type is then classified into three major groups (1-3) of increasing severity, and further into subgroups and specifications based on morphology (Magerl et al. 1994). Therefore, fractures are graded from definitely stable to definitely unstable. The thoracolumbar injury classification and severity score (TLICS) was devised to assist in clinical decision making in terms of the need for operative versus non-operative care and a surgical treatment approach in unstable injuries (Vaccaro et al. 2005). In addition to radiographic appearance of the morphology of the injury, the TLICS takes into account the integrity of the posterior ligament complex, and the presence of a neurological injury (Vaccaro et al. 2005). At present, the TLICS is considered the most clinically relevant classification system, because of its verified high interobserver reliability and incorporated high-risk characteristics for instability (Patel et al. 2007, Koh et al. 2010).

In deformities, the magnitude of the deformity is determined by the method of Cobb (Cobb 1948). The Cobb angle is defined by the angle of two endplates of vertebrae; it is an objective radiographic parameter to appraise the curve severity and the risk of progression, and the need and success of treatment of scoliosis (Cobb 1948). In adolescent idiopathic scoliosis, if the Cobb angle exceeds a threshold of 50° at completion of growth, spinal instrumentation facilitating fusion is advised, particularly when a risk of progression remains (Weinstein et al. 2008, Negrini et al. 2012, Kotwicki et al. 2013). Also, the aesthetic aspect plays a role in the decision. In adult spinal deformities, a through diagnostic work-up needs to be done to reveal the specific problem and potential pain sources. If back pain is the leading symptom, fusion is usually indicated (Aebi 2005). Also, the progression of the curve may be an indication for surgical treatment (Bradford 1988, Aebi 2005). If an isolated decompression is done at the apex of the degenerative curve or at the bottom of a rigid curve, progression of the curve is very likely and the decompression should be accompanied by fusion (Aebi 2005). The Meyerding classification defines the degree of spondylolisthesis as the percentage of slippage of a vertebral body relative to an adjacent vertebral body (Meyerding 1956). In spondylolisthesis of children and adolescents, spinal fusion is indicated with Meyerding grade II (26–50 % of slippage) with persistent symptoms despite six months of conservative treatment (Wiltse 1961, Wiltse et al. 1976, Attiah et al. 2014). Usually, the evidence of slippage progression, particularly in dysplastic (type I) spondylolisthesis, and any neurologic deficit are also indications of spinal fusion (Wiltse 1961, Attiah et al. 2014). Further,

fusion is always indicated in grades III-IV (> 50 %) spondylolisthesis (Wiltse 1961, Attiah et al. 2014).

Primary bone tumours of the spine and spinal metastases may lead to spinal instability and/or progressive deformity due to bony destruction and/or fractures. Moreover, resection of bony tumours may result in the same problems, which are indications of spinal fusion (Patchell et al. 2005). Further, the resection of the dumbbell tumours, with their contiguous anatomic space components, may necessitate extended laminectomies and graded or complete facetectomies (Asazuma et al. 2004, Gottfried et al. 2005). The involved aggressive bone removal may cause mechanical instability in the spine, which is then an indication for fusion surgery. In spinal infections, symptoms related to existing spinal instability or progressive deformity, and prevention of development of these, are also indications for spinal fusion. After radical debridement, instrumented fusion has safely been performed in a variety of spinal infections (e.g. pyogenic vertebral osteomyelitis, pyogenic and tuberculosis spondylitis) (Benli et al. 2003, Chen et al. 2007, Korovessis et al. 2008).

In addition to the changes in the FSU biomechanics related to ageing, changes in the sagittal alignment of the spine due to postural alterations of ageing may also alter load distribution in each spinal segment (Boden et al. 1996, Hammerberg et al. 2003, Boulay et al. 2006, Barrey et al. 2013). The progressive degeneration of discs and facet joints may result in osteophyte formation, ligamentum flavum hypertrophy and calcification, and subsequent spinal stenosis, spondylolisthesis, and, in some patients, symptomatic degenerative scoliosis (Faldini et al. 2013). Essentially, joint pain related to degenerative changes and joint deformities can be treated by fusion (Hanley 1995).

Pain associated with degeneration of facet joints is usually characterized by improvement during motion, and aggravation in extension and rotation (Jackson 1992). Otherwise, mechanical low-back pain of segmental instability can be produced by motion, particularly by vibration and sudden movements, and is facilitated during rest. Clinical signs of instability in the lumbar spine are: inability to bend forward and return to an erect position due to a sudden attack of low-back pain (instability catch), drop of a straightened leg on the examination table due to a sudden attack of low-back pain (painful catch), and anxiety about the sensation of collapse of the low-back pain due to a sudden attack of low-back pain during movement (apprehension) (Kirkaldy-Willis et al. 1982, Kotilainen et al. 1993). The radiographic segmental mobility of symptomatic patients with spondylolisthesis is most accurately revealed by radiographs in standing and re-

cumbent position in terms of sagittal translation, and by flexion-extension radiographs in standing position in terms of sagittal rotation (Cabraja et al. 2012).

When the origin of pain is proved to lie within the FSU of spine and when non-operative treatment of pain fails, spinal fusion is indicated to eliminate painful motion (Allen et al. 2009, Phillips et al. 2013). Particularly, severe facet joint osteoarthritis and disc degeneration with severe endplate abnormalities (Modic types I and II) may predict a favourable fusion outcome (Weishaupt et al. 1998). Instead, two recent studies show that fusion is not indicated for lumbar spinal stenosis without or with degenerative stable spondylolisthesis when no overt instability is present (Forsth et al. 2016, Ghogawala et al. 2016, Peul et al. 2016). The development of spinal instability with or without subsequent deformity may also be a consequence of iatrogenic disruption of posterior tension band, paraspinal muscles and facet joint complexes. The purpose of this doctoral thesis is focused on the degenerative disease in the lumbar region.

### *2.1.4 Surgical methods*

The identification of the unstable FSU preceding the surgery may be challenging, but is of vital importance for the outcome (Stokes et al. 1987, Pope et al. 1992, Okawa et al. 1998). The length of spinal fusion must be balanced to minimize the number of fused FSUs, and to provide sufficient stabilization at the same time. For a successful outcome, the spine pathology in question with its biomechanical characteristics should also be taken into consideration in planning the fusion method. The aim of the spinal fusion is to produce a solid bony contact beyond the unstable FSUs.

Lumbosacral fusion can be attained by three approaches (Hoover 1968). The most commonly used method is posterolateral fusion (PLF) consisting of bone graft application on the posterior spine structures. Alternatively, bone graft can be applied into the intervertebral space for interbody fusion after removal of the disc and preparation of endplates by either the anterior (ALIF), transforaminal (TLIF), extreme lateral (XLIF) or posterior approach (PLIF). The combination of posterolateral and interbody fusion methods is called a 360-degree fusion. Beyond the approach-based division, minimally invasive surgery (MIS) techniques have been developed to reduce approach-related morbidity while meeting the same goals as the conventional open procedure (Foley et al. 2003, German et al. 2005, Stevens et al. 2006).

Spinal instrumentation means the implantation of devices attached to the spine to provide spinal stability and thus facilitate ossification. The instrumented hardware should bear the directed mechanical forces until the solid fusion has occurred. According to the Cochrane database review of surgery for degenerative lumbar disease, 31 randomized controlled trials were found in March 2005 (Gibson et al. 2005). The studies on the clinical effectiveness of fusion showed conflicting results, but eight studies pointed out that instrumented fusion produced higher fusion rates that non-instrumented, though any improvement in clinical outcomes was probably marginal (Gibson et al. 2005).

#### *2.1.4.1 Posterolateral fusion*

In general, the posterolateral fusion (PLF) approach consists of decortication of the posterior aspect of the transverse processes, pars interarticularis and facet joints, and subsequent application of bone graft on the decorticated surfaces and in the facet joints from a midline incision. Alternatively, the approach can be carried out bilaterally through two paramedian skin incisions over the fascial plane that separates the multifidus and longissimus muscles following fascial incision further to the facet joints (Wiltse et al. 1968). If neural structures are compressed, decompression is usually performed prior to the fusion to obtain local autologous bone graft material for the fusion.

PLF can be performed either with or without posterior internal fixation. In fixation, the pedicles are the strongest points of attachment to the spine. Further, the pedicle screws have proven to have the greatest pullout strength compared to the sublaminar cables or hooks (Hitchon et al. 2003, Tai et al. 2014). The core diameter of the pedicle screw specifies the screw strength and the outer diameter correlates with the screw pullout. The addition of pedicle screws has been proven to increase the fusion rate compared to only PLF (Boos et al. 1997, Gibson et al. 2005, Angevine et al. 2007). For instance, Mardjenko et al. (1994) reported that the fusion rates increased from 86 % with only PLF to 96 % with the addition of pedicle screws in their meta-analysis, when treating degenerative spondylolisthesis. In a historical cohort study of 2176 cases of degenerative spondylolisthesis, the fusion rate with uninstrumented posterolateral fusion was 75 %, and with addition of pedicle screws 83 % (Yuan et al. 1994).

Since the placement of pedicle screws, the connecting rods are secured into place by locking nuts after distraction or compression (Figure 1). Cross-linked devices can be used to link the parallel rods together (Figure 2). Until recent years, pedicle screw instrumentations manufactured of titanium alloy have been

installed. However, the fatigue life of titanium alloy is limited, and the titanium alloy constructs fail at the notch induced by, e.g. rod contouring (Nguyen et al. 2011). Further, the stiffness of the traditional pedicle screw instrumentation of titanium alloy has been shown to be even 20 times greater than that of bone, possibly causing stress at the bone-implant interface, and inducing bone resorption at the site (Kang et al. 2017). Despite the high stiffness of the cobalt chromium (CoCr) alloys, the cyclic load testing of the screws and rods of CoCr alloy has revealed CoCr alloy constructs to have significantly longer fatigue life than titanium alloy constructs (Nguyen et al. 2011). Recently, non-metallic carbon-fiber-reinforced polyetheretherketone (CFR-PEEK) spinal implants have been developed in order to overcome the disadvantage of a metal-induced imaging artefact, and, by allowing limited motion, to better approximate the normal biomechanics of the spine via increased anterior column load-sharing, to reduce the rate of adjacent segment disease and implant failure rates (Mavrogenis et al. 2014, Chou et al. 2015, Kang et al. 2017, Lindtner et al. 2018).

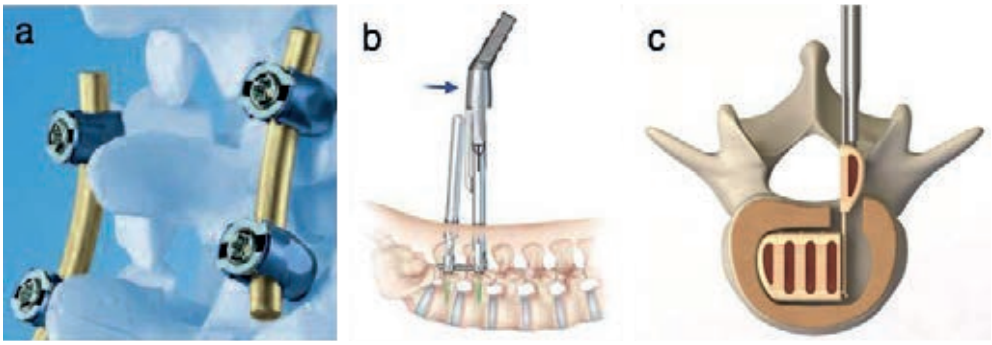


Figure 1 (a) Transpedicular lumbar fusion with the Pangea® Spine System, (b) minimally invasive placement of rod through two stab incisions with the Viper® MIS Spine System, and (c) minimally invasive insertion of modular cage for interbody fusion with the InterFuse® T-cage (with permissions of DePuy Synthes Nordic (a and b) and VTI (c)).

The advantages of PLF are the relatively simple technique, the possibility to perform a concomitant decompression and avoidance of visceral and vascular complications associated with anterior approaches (Polly et al. 2005). The demand for extensive muscle dissection causing postoperative pain and profuse blood loss is the major disadvantage of PLF (Campbell et al. 2017). In the region of the mobile lumbar spine, PLF is more difficult to achieve than interbody fusion due to difficulties in placing the posterolateral bone graft under compression (Suk et al. 1997, Ha et al. 2008, Abdu et al. 2009, Fujimori et al. 2015, Campbell

et al. 2017). Disadvantages related to pedicle screw instrumentation have been reported to be a relatively high risk especially for nerve and vascular injury complications, hardware failures, and a predisposition to infections due to the operation technique and the foreign body nature of the instrumentation (Blumenthal et al. 1993b, Lonstein et al. 1999, Jutte et al. 2002, Katonis et al. 2003).

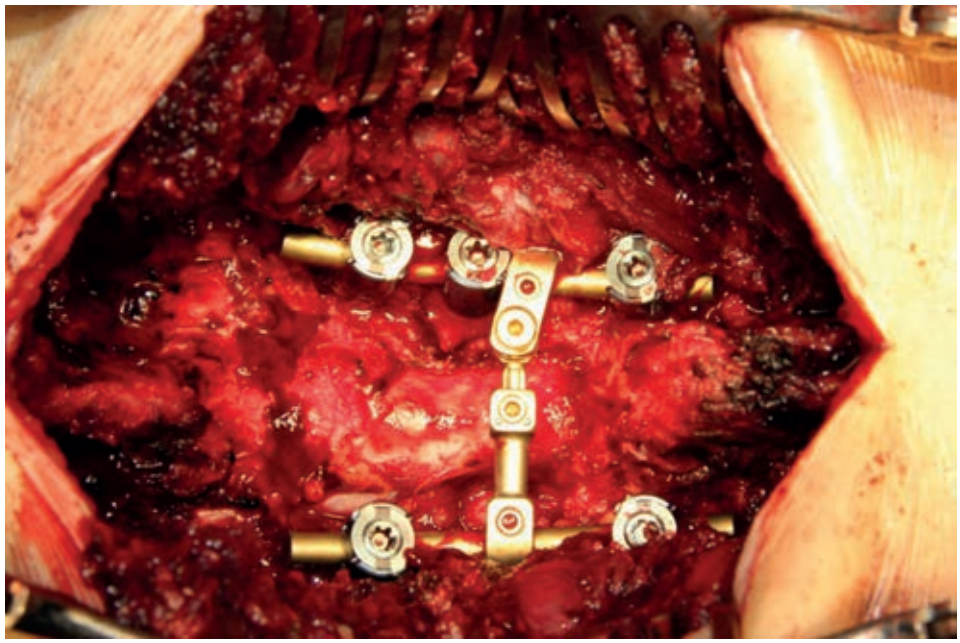

Figure 2 Transpedicular lumbar fusion with a cross-linked device linking the parallel rods together (by courtesy of Dr. Esa Kotilainen).

#### *2.1.4.2 Interbody fusion*

At present, structural implants, usually synthetic cages have become a standard part of interbody fusion procedure, because they increase fusion rates by supporting the anterior column from collapsing, and by preventing the graft material from migration, until the bone graft unites the bone of the opposing prepared vertebral endplates (DeBowes et al. 1984, Brantigan et al. 1991, Hanley et al. 1999, Cole et al. 2009). All approaches to achieve interbody fusion may be supplemented with the pedicle screw instrumentation and PLF to increase the stability of the construct and the fusion rate (Brodke et al. 1997, Cole et al. 2009).

The open PLIF procedure is carried out through a posterior midline incision and continued with a laminotomy and possible resection of the medial part

of the facet joints to expose the exiting and traversing nerve roots and lateral extent of the disc space (Kai et al. 2004, Cole et al. 2009, Talia et al. 2015). The dorsal third of the interspinous ligament may be preserved as a posterior tension band (Cole et al. 2009). The thecal sac and traversing nerve roots are decompressed and retracted medially to expose the disc space. A complete discectomy is performed bilaterally, and the cartilaginous endplates are prepared. However, the disc height may be restored by the use of distractors with serially increasing heights. The disc space is packed with graft material from the contralateral side. Thereafter, a lordotic hollow cage of, e.g. titanium, carbon fiber or PEEK is filled with graft material (Figure 1) and placed on the contralateral side under a compressive load to improve fusion. Finally, more graft material is placed on the ipsilateral side. The position of the implant is confirmed with imaging.

The open TLIF procedure differs from the open PLIF technique in that it is usually performed unilaterally on the symptomatic side or on the side of anatomical abnormalities (Rosenberg et al. 2001). Generally, a more extensive facetectomy is needed than with the PLIF technique to open the transforaminal window (Talia et al. 2015). In a unilateral approach, the gradual distraction of disc space can also be accomplished by using the pedicle screws (Cole et al. 2009). However, the decompression of the neural elements is indirect on the contralateral side. Due to the extensive facetectomy, the retraction of the thecal sac can be minimized while inserting the cage, and hence the risk of an incidental durotomy, neurological injury and chronic radiculopathy is decreased compared with the PLIF approach (Rosenberg et al. 2001, Cole et al. 2009). The other advantages of the TLIF procedure compared with PLIF include improvement in lordotic alignment because of the unlimited graft placement within anterior column, and preservation of posterior column integrity for support and also providing increased surface area for fusion though minimizing lamina, facet and pars interarticularis resection in total (Lonstein et al. 1999, Cole et al. 2009). Several studies have reported higher complication and incidental durotomy rates, and longer operative times with PLIF compared to TLIF (Humphreys et al. 2001, Sakeb et al. 2013, Zhang et al. 2014).

In the ALIF technique, several different skin openings can be used. An anterior vertical paramedical approach can be accessed to all lumbar levels, but a horizontal (Mini-Pfannenstiel) approach may be preferred for L5/S1 level (Mobbs et al. 2015). The rectus abdominis muscle is mobilized and a retroperitoneal corridor is created into the prevertebral space. The prevertebral blood vessels, ureter and spermatic cord in males are identified and mobilized when necessary. For ALIF, stand-alone cages may be supplemented with an anterior vertebral plate, locking screws and a threaded cylinder to avoid the application of the

posterior instrumentation (Chen et al. 2013). The ALIF technique provides direct access to the ventral surface of vertebral bodies and intervertebral spaces, permitting a more complete and efficient disc excision and endplate preparation compared to PLIF or TLIF (Talia et al. 2015, Mobbs et al. 2015). Thus, the implant size and its surface area can be maximized further, enabling a more extensive correction of lumbar lordosis and restoration of the foraminal height (Mobbs et al. 2015). Also, ALIF leaves the posterior paraspinal muscles intact, thus reducing postoperative pain and disability. On the other hand, the approach-related risks include direct vascular and visceral injuries, deep venous thrombosis and retrograde ejaculation in males. Compared to TLIF, ALIF has been shown to be superior in capacity to restore disc and foraminal height, and lumbar lordosis (Hsieh et al. 2007, Kim et al. 2010, Phan et al. 2015, Teng et al. 2017). However, a lower rate of incidental durotomies, and a higher rate of blood vessel injuries have been reported in ALIF procedures (Phan et al. 2015).

In a recent systematic review and meta-analysis on degenerative spondylolisthesis, no statistically significant difference was found in functional and operative outcomes with PLF compared to PLIF or TLIF when the majority of the patients with PLF had an instrumented fusion (Campbell et al. 2017). In five of six studies that satisfied the inclusion criteria reporting fusion results of a total of 579 patients, the fusion rate ranged between 84 and 95 % in instrumented PLF and 87 and 100 % in PLIF or TLIF, respectively (Ha et al. 2008, Abdu et al. 2009, Fujimori et al. 2015, Gottschalk et al. 2015, Kuraishi et al. 2016). In pooled data of the studies, the fusion rates of instrumented PLF, and PLIF or TLIF are 87 % and 93 %, respectively. These results are well consistent with the fusion rates of other studies (Fritzell et al. 2002, Polly et al. 2005, Sivaraman et al. 2015).

#### *2.1.4.2.1 Subsidence*

Subsidence of an interbody implant is usually defined as a sinking into either of the adjacent vertebral endplates of at least 2–3 mm in lumbar spine (Kumar et al. 1993, Chen et al. 2005, Isaacs et al. 2016). Subsidence may be related to surgical technique, implant self and bone quality of the patient (Vaidya et al. 2008, Hou et al. 2009, Le et al. 2012). Through overdistraction, too high implant size can contribute to subsidence. On the other hand, an increase in contact area of an implant has shown to cause a statistically significant decrease in the rate of subsidence (Hou et al. 2009, Lee et al. 2010, Le et al. 2012). Also, implant morphology, structure and material are important factors in subsidence (Lowe et al. 2004,

Vaidya et al. 2008, Le et al. 2012). Subsidence may defeat the purpose for which the interbody fusion has been initially performed, resulting in loss of disc height and subsequent loss of ligamentous stability, as well as in return of foraminal stenosis and ensuing foraminal stenosis (Vaidya et al. 2008, Tokuhashi et al. 2009). At the critical lumbar levels of L4/5 and L5/S1, subsidence may also cause the loss of lordotic correction, and consequently sagittal imbalance (Chen et al. 2005, Malham et al. 2017). Clinical subsidence refers to radiological subsidence with recurrent pain, neurological symptoms, or a significant decline of clinical outcome measures related to loss of indirect neural decompression (Le et al. 2012). Subsidence has been shown to develop mostly within six months postoperatively (Kim et al. 2013). The rate of subsidence has been reported to be the highest at the most superior lumbar level (L1/L2), and decreased progressively at L2/3 and L3/4 levels (Le et al. 2012). Subsidence is directed to the superior of the adjacent endplates in 70 % of the cases (Le et al. 2012). In previous studies, the rate of radiological subsidence with various definitions has ranged between 3 and 28 % when using intervertebral cages of different materials (Chen et al. 2005, Vaidya et al. 2008, Lee et al. 2010, Youssef et al. 2010, Le et al. 2012, Isaacs et al. 2016).

#### *2.1.4.3 Minimally invasive approach for lumbosacral fusion*

Recently, minimally invasive (MI) spine surgery (MISS) have been introduced in order to reduce approach-related morbidity through the use of the smallest possible access ports, while meeting the same goals of the open procedure (German et al. 2005). The advantages of MI-fusion compared to open procedures include reduced intraoperative blood loss, decreased postoperative pain, more rapid postoperative ambulation, shorter length of hospitalization and faster recovery (Dhall et al. 2008, Chaudhary et al. 2011, Jin-Tao et al. 2015, Khan et al. 2015, Goldstein et al. 2016, Lu et al. 2017). Also, two systematic reviews pointed out both direct and indirect cost savings in favour of MI-fusion with total savings of 2.5–49.3 % compared to open fusion (Al-Khouja et al. 2014, Goldstein et al. 2016). To overcome the dearth of anatomical landmarks in MI-fusion surgery, image guidance and intraoperative navigation are of great value (Wood et al. 2010).

The MI-TLIF procedure is a variant of open TLIF based on a paramedian Wiltse-type approach. An expandable tubular or a mini-open retractor can be used to access the posterior elements through an approximately 3-cm skin incision on the symptomatic side (Karikari et al. 2010). After insertion, the retractor is mounted onto the table. Next, decompression, discectomy, and bone graft and

cage placement are performed unilaterally. Ipsilateral pedicle screws are fastened through the initial incision, but contralateral screws are usually inserted through separate 2-cm stab incisions under image guidance (Karikari et al. 2010). Finally, the connecting rods are secured into the screws by locking nuts and linked to each other when required (Figures 1 and 3). The MI-TLIF approach limits the harvested volume of local bone graft.

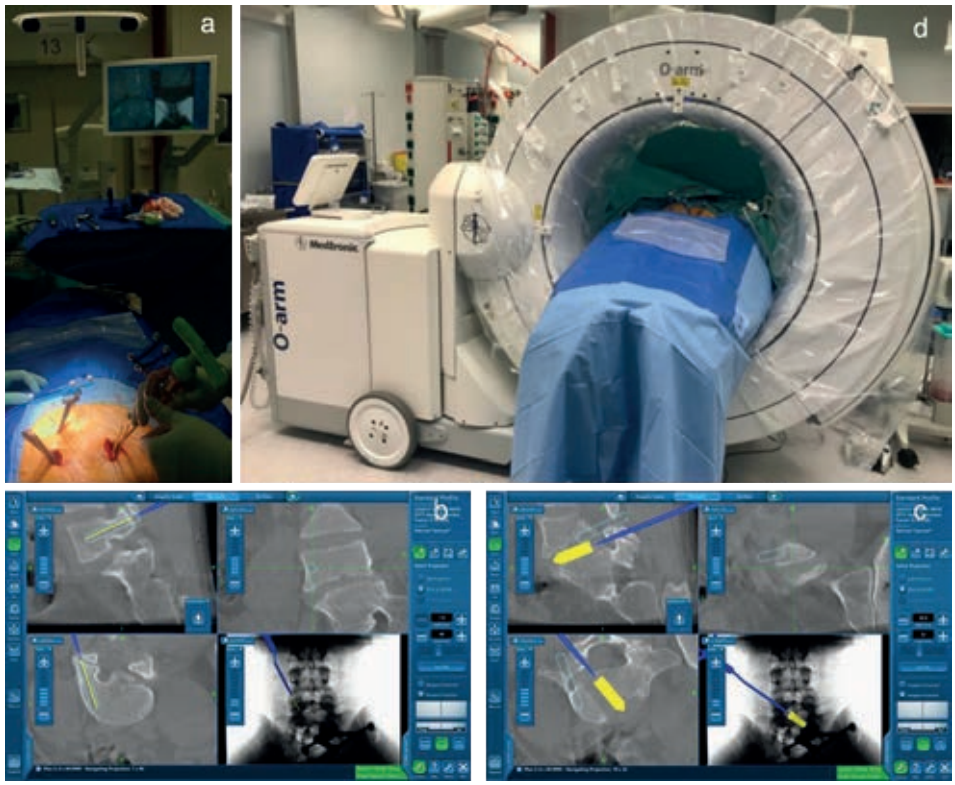


Figure 3 (a) Minimally invasive placement of pedicle screw using spinal navigation with the StealthStation® S7® Navigation System, (b) navigation of left L5 pedicle screw, (c) navigation of L5/S1 level interbody implant, (d) intraoperative 3D control imaging with the O-arm® Imaging System.

The MI-fusion procedure is reported to associate with a deep learning curve (Jin-Tao et al. 2015). No specific approach-related complications of MI-fusion have been identified. The complications can be divided into technical complications, such as incidental dural tears and screw malposition, and infection complications, such as superficial wound infection (Hu et al. 2016). Moreover, systemic complications, such as pneumonia, urinary tract infection and deep venous thrombosis occur. According to two meta-analyses and a systematic review,

the complication rate ranged between 12.6 and 23.2 % for open TLIF and between 7.5 and 16.5 % for MI-TLIF (Wu et al. 2010, Khan et al. 2015, Hu et al. 2016). The results of all three above studies demonstrate a significantly lower rate of complications in MI-TLIF patients compared to open fusion patients (Wu et al. 2010, Khan et al. 2015, Hu et al. 2016).

The fusion rate can be evaluated with different radiological modalities and criteria (e.g. bridging interbody bone, absence of continuous interbody radiolucency lines and lack of motion on lateral flexion-extension radiographs) that may complicate the comparison of results from different studies (Park et al. 2007, Wu et al. 2010). The comparison of open and MI-fusion fusion results is also difficult because of pseudoarthrosis, and implant failure rates depend on several variables, which are not related to the approach type. Such variables are, e.g. type, size and material of the implant, fusion enhancing substances used, quality and extent of endplate and posterior fusion area preparation, existence of posterolateral bone graft, quality of hardware construction and positioning, the presence of comorbidities, bone quality, follow-up time, and the number of levels fused. In various comparative studies, the reported fusion rate with open PLIF/TLIF varied between 90.0 and 98.5 % and with MI-PLIF/MI-TLIF between 90.0 and 97.5 % (Park et al. 2007, Peng et al. 2009, Wu et al. 2010, Lee et al. 2012, Seng et al. 2013, Gu et al. 2014, Jin-Tao et al. 2015, Serban et al. 2017). The individual studies reported conflicting results with each other, of which, open or MI-fusion was superior in the fusion rate.

### *2.1.5 Radiological evaluation*

Pseudoarthrosis is defined as the presence of symptomatic bony non-union at least a year after spinal fusion surgery (Larsen et al. 1997). It can result in motion of the operated FSUs with correlative signs and symptoms of spinal instability. Non-union then means a permanent failure of the intended bone growth across a FSU. Clinical manifestations of spinal non-union can range from asymptomatic to construct failure, and subsequent spinal deformity and neurological injuries. Usually, the asymptomatic radiological non-union does not warrant surgical treatment (Selby et al. 2012).

Historically, the standard for assessment of spinal fusion has been open surgical exploration and direct examination, which still today remain the most accurate way to determine fusion (Hilibrand et al. 1998, Buchowski et al. 2008, Selby et al. 2012). Of non-invasive assessment methods, plain static radiographs have traditionally been the most commonly used method for evaluation of spinal

fusion. In plain radiographs, indicators of non-union include graft resorption, implant subsidence or migration, implant breakage, and presence of deformity under physiological loads (Selby et al. 2012). Their advantages are relatively low cost, ease of administration and relative safety (Selby et al. 2012). When comparing surgical exploration with plain radiographs to detect bony fusion in combined interbody and PLF, only 69 % overall agreement was demonstrated (Blumenthal et al. 1993a). In flexion-extension radiographs, the absence of movement has been shown to not always correlate with a solid fusion (Santos et al. 2003). Conversely, solid, but yet incomplete interbody or PLFs may allow a large amount of movement (> 5 °) as a result of inherent elasticity of bone (Selby et al. 2012). Compared with fine-cut computed tomography (CT), both plain and flexion-extension radiographs have been shown to overestimate the fusion rates (Santos et al. 2003, Carreon et al. 2007b, Selby et al. 2012).

CT is nowadays widely accepted as the imaging modality of choice for non-invasive assessment of spinal fusion (Selby et al. 2012). A distinct advantage of CT in determining solid fusion is its ability to distinguish trabecular bridging bone (Pai et al. 2006). Advances in CT technology, such as fine-cut CT with 0.5–1 mm slices, helical acquisition, multiplanar reconstruction and artefact reduction, have recently significantly improved the ability to assess fusion on CT scans (Santos et al. 2003, Pai et al. 2006). Compared with surgical exploration, fine-cut CT scans have proved to have 89 % probability to correctly demonstrate PLF (Carreon et al. 2007a). Fine-cut CT scans have also been presented to demonstrate "locked pseudoarthrosis" meaning a non-union within an interbody cage that may still be a mechanically stable construct (Santos et al. 2003). The agreement between the combination of plain and flexion-extension radiographs, and CT scans in evaluating lumbar PLF has been demonstrated to be only 46–59 % (Carreon et al. 2007b). In the same study, the degree of interobserver and intraobserver agreement was shown to be considerably greater with modern fine-cut CT scans than with plain and flexion-extension radiographs (Carreon et al. 2007b). The disadvantages of CT include the interpretation difficulties of scans with metal artefacts, and potential harm from ionizing radiation to the patient.

Various grading systems have been introduced to evaluate fusion (Lenke et al. 1992, Brantigan et al. 1993, Bridwell et al. 1995, Molinari et al. 1999, Glassman et al. 2005, Fogel et al. 2008, Isaacs et al. 2016). The Bridwell four-level fusion grading system used to assess interbody and posterior fusion with plain radiographs has been quite extensively used. However, the system has shown to result only in fair interobserver and intraobserver agreement (Newton et al. 2005). When the interbody fusion grades I and II are combined to comprise fusions > 50 % of the disc space and compared with grades III and IV of fusion <

50 % of the disc space, a substantial interobserver and intraobserver agreement was reached (Newton et al. 2005). CT scans are needed to evaluate the interbody fusion in the more recent grading systems, like in the modified method of Brantigan and Steffee to describe the Fraser definition of locked pseudoarthrosis (BSF scale), and in the bridging bone grading scale of Isaacs et al. (Fogel et al. 2008, Isaacs et al. 2016).

Bone graft substitutes, extenders and biological agents for promoting spinal fusion are either radiopaque (e.g. calcium phosphate ceramics, calcium sulphate, bioactive glasses) or radiolucent (e.g. demineralized bone matrix, recombinant human bone morphogenetic protein 2 (rhBMP-2)) on postoperative radiographs and CT scans (Selby et al. 2012). Based on an early study, implanted β-tricalcium phosphate ceramics can be visible on radiographs up to six months postoperatively (Lerner et al. 2009). Thus, when ceramic materials are used, at least early assessment of fusion may be confounded by their radiopaque appearance (Selby et al. 2012). No radiological method is so far available to reliably distinguish ceramics and newly formed bone. At the moment, a research group at the University of Helsinki is developing a precise 3D imaging method that will be able to distinguish both ceramics and newly formed bone (Heino 2018, and N. C. Lindfors, personal communication, April 25, 2018).

### *2.1.6 Clinical outcome measures*

Despite the achievement of successful bony fusion on the radiological assessment, the clinical result may be poor and vice versa (Santos et al. 2003, Djurasovic et al. 2011). Several studies have shown a lack of correlation between radiological fusion rate of spinal fusion with or without instrumentation and clinical success (Herkowitz et al. 1991, France et al. 1999, Fritzell et al. 2002, Lamberg et al. 2005). However, several other studies have shown that presence of radiological pseudoarthrosis correlates with poorer clinical outcome (Kornblum et al. 2004, Resnick et al. 2005, Champain et al. 2007, Djurasovic et al. 2011). As limitating factors, many of the above studies used a subjective surveyor-based assessment of clinical outcome, and almost all used only plain radiographs to assess the fusion rate. Also, validated health-related quality of life (HRQOL) measures have turned out to be a more patient-driven method of assessing clinical outcomes (Asadi-Lari et al. 2004, Djurasovic et al. 2011). In a study evaluating the fusion rate by CT scans, assessed solid fusion was shown to contribute to clinical outcome (Djurasovic et al. 2011).

Particularly in spine surgery, the treatment outcome is influenced by multivariable, also non-morphological factors, and thus requires well-designed, standardized and validated outcome tools to cover various fields of outcome (Mannion et al. 2006). Back pain is the most common reason for spinal fusion surgery, and therefore pain relief is an essential means to measure the outcome of a specific therapy (Haefeli et al. 2006). No consensus about the definition of chronic pain exists, but in earlier studies it is defined by duration as between four weeks and more than a year of persistent pain (Raspe et al. 2003). The experience of pain is largely individual and difficult to assess objectively. Besides the quite easily estimated pain intensity, pain affect is more complex and may be defined as the emotional arousal or disruption engendered by the sensory experience of pain (Von Korff et al. 2000). Changes in the emotional component of pain correlated better to changes in verbal rating scales (VRS) of pain than to changes in pain intensity measures (Von Korff et al. 2000).

The visual analogue scale (VAS) is a straight line with the ends defined as the extreme limits of the sensation, such as ”no pain” and ”the worst possible pain” (Scott et al. 1976). The graphic rating scale (GRS) additionally uses descriptive terms, such as ”mild”, ”moderate”, ”severe” or a numerical scale on a 10 or 15 cm long line (Seymour et al. 1985). VAS and GRS have been demonstrated to be sensitive to treatment effects and found to correlate positively with other self-reporting measures of pain intensity (Kremer et al. 1981, Seymour et al. 1985, Jensen et al. 1989). In addition to measuring the pain intensity levels by adjectives, VRS including statements of behavioural parameters can be used as the behavioural rating scale. To evaluate pain verbally, e.g. in telephone interviews, the numerical rating scale (NRS) can be used (Von Korff et al. 2000). Moreover, VRS and NRS have been shown to correlate with other pain assessment tools (Kremer et al. 1981, Jensen et al. 1989).

The most commonly used instruments to evaluate disability caused by low back pain are the 24-question Roland-Morris Disability Questionnaire (RMDQ) and the ten-item Oswestry Disability Index (ODI), both validated for several languages (Roland et al. 2000). In each item or question, the ODI has six response possibilities, whereas RMWQ has only a dichotomous possibility to answer. Based on several studies, the RMDQ detects changes over time more sensitively than the ODI, particularly in patients with minor disabilities (Hsieh et al. 1992, Stratford et al. 1994, Beurskens et al. 1996). By contrast, the detailed scale of ODI allows the assessment of even subtle changes of disability, and is recommended for use with patients who may have persistent severe disability over a period of measurement (Roland et al. 2000).

In the field of spinal surgery, the instruments assessing the quality of life are used in combination with disease-specific pain and disability tools. According to the World Health Organization's (WHO) definition of quality of life, its Quality of Life questionnaire (WHOQOL), the Medical Outcome Study (MOS) SF-36/-12/-8 and EuroQol questionnaires should cover individuals' perception of their position in life in relation to their goals, expectations, standards and concerns in the context of the culture and value systems in which they live. The WHOQOL consists of a hundred questions covering six domains of physical and psychological health, level of independence, social relationships, environment and spirituality/religion, each question having a five-point answering scale (Whoqol 1994). Built for clinical use, a core questionnaire, WHOQOL-Bref consisting of 24 items, has shown validity and reliability (Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. 1998).

The widely used, standardized and validated SF-36 questionnaire includes 36 items with eight scales to describe quality of life on five-point scales: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health (Garratt et al. 2002). Later, a twelve-item SF-12 and an eight-item SF-8 have been constructed to improve efficiency and practicability in the clinical setting (Ware et al. 1996). The other self-completion tool EQ-5D with four components for the assessment of standardized non-specific quality of life consists of two health-related and two background information parts, and the GRS (Brooks 1996). The EQ-5D has been shown to be less sensitive and more susceptible to the ceiling effect (i.e. at low levels of perceived health) than the SF-36, which better detects changes over time (Brazier et al. 1993). The Psychological General Well-Being Index (PGWBI) assesses psychological distress (Dupuy 1984). Recently, WHO has developed a holistic tool to accurately identify and understand the impact of a disease on a patient, called the International Classification of Functioning, Disability and Health (ICF). The ICF utilizes domains of body functions and structures, activities and participation, as well as environmental and personal factors (Vargus-Adams et al. 2014). In a study with patients having undergone lumbar fusion, the domains of ICF, which were most frequently used to assess the patient's experiences, activity and participation, and environmental factor, were recognized (Abbott et al. 2011).

The disease-specific four-step Odom's criteria were originally developed to grade the outcome of a patient (i.e. "patient success") after cervical disc lesion operations (Odom et al. 1958). Later, the widely used criteria, which assess the improvement in the physical symptoms and the ability to perform daily activities after a treatment, have been modified to cover the lumbar spine (Epstein 2006,

Angevine et al. 2007). Also, a correlation between Odom's criteria and the VAS and the ODI has been detected (Zoëga et al. 2000).

## 2.2 Pedicle screw position accuracy

### *2.2.1 Pedicle screw positioning methods*

The placement of pedicle screws may be technically demanding due to the complex three-dimensional anatomy of the vertebra. Although the pedicles have been measured to be widest at the L5-level, they are narrower in the superior lumbar spine than in the inferior thoracic spine (Lien et al. 2007, Ofiram et al. 2007). Different morphometric widths of the superior lumbar pedicles are listed in Table 1. The measurements of Lien et al. (2007) are derived from the Taiwanese population. The best screw diameter is estimated to be about 65–80 % of the pedicle diameter (Flynn et al. 2013).

Lien et al. (2007) also reported the anatomic distances of the lumbar and inferior thoracic pedicles to the nerve roots and to the thecal sac. In the lumbar spine, the inferior distance from the pedicles to the nerve roots and the medial distance to the thecal sac were shown to be the shortest, both may be on average < 2.0 mm (Lien et al. 2007). The shortest superior mean distances to the nerve roots were 4.1 mm and lateral mean distances 2.4 mm, in the lumbar spine (Lien et al. 2007). With deviating spinal curvature, when the thecal sac is locally shifted towards the concave side of the spine, the safety marginal may even be decreased (Karapinar et al. 2008). Also, the rate of pedicle screws positioned inside the pedicle cortices has been shown to be significantly lower in patients with coronal plane spinal deformity than without it (Belmont et al. 2002). Thus, e.g. a combination of degenerative scoliosis, a narrow pedicle of the superior lumbar spine and a short distance to a nerve root or to thecal sac may make a pedicle screw positioning extremely difficult.

A greater degree of pedicle breach has proved to lead to a greater loss of axial pullout strength of the screw, particularly if the breach is in the superior or inferior direction, and subsequent risk for early screw loosening or failure (Costa et al. 2013, Stauff 2013). For the above reasons, the insertion of pedicle screws requires technical accuracy to ensure their clinical effectiveness, and to avoid neural and vascular injuries as a result of screw insertion error. Technical expertise of the instrumentation and mounting technique, and familiarity with the spi-

nal anatomy is needed from the surgeon to overcome these issues. The technical goal is to place a maximum diameter and length screw perfectly within the cortical borders of the pedicle and the vertebral body (Gautschi et al. 2011, Stauff 2013). However, the insertion itself can be carried out using several approaches and techniques, and with or without utilization of modern facilities, e.g. spinal navigation, intraoperative imaging, and neuromonitoring techniques.

Table 1 Examples of previous morphometric studies on the lumbar pedicle widths at the L1 and L2 levels (SD: standard deviation, CI: confidence interval).

| Reference | Level | Range (mm) | Mean (mm) | SD (mm) | 95 % CI (mm) |
|---|---|---|---|---|---|
| (Zindrick et al. 1987) | L1 | 4.5–13.0 | 8.7 | 2.3 | - |
| | L2 | 4.0–13.0 | 8.9 | 2.2 | - |
| (Lien et al. 2007) | L1 | - | 6.5 | 1.7 | - |
| | L2 | - | 7.2 | 1.8 | - |
| (Ofiram et al. 2007) | L1 | 2.4–12.2 | 6.0 | 1.6 | 2.8–9.2 |
| | L2 | 3.1–10.8 | 6.2 | 1.5 | 3.3–9.2 |

The conventional methods include the use the dorsal anatomical landmarks, i.e. the freehand technique, laminoforaminotomy for each screw and/or extensive use of multiplanar x-ray or fluoroscopy (Rampersaud et al. 2007, Karapinar et al. 2008). The image-guided navigation or computer-assisted surgery (CAS) is computer-based surgical technology that links image data with corresponding surgical anatomy (Murphy et al. 1994, Kalfas et al. 1995). Depending on the modality of the imaging used for reference, it provides the surgeon with the ability to guide multiplanar, either 2-dimensional (2D) or 3-dimensional (3D) fluoroscopic or CT images during the procedure; this enhances orientation to nonvisualized spinal anatomy (Kalfas et al. 1995). The progress of technology to exploit intraoperative imaging in navigation has, e.g. decreased the influence of the position of the mobile spine during imaging on the accuracy of navigation (Ling et al. 2014). In addition, neuromonitoring using free-run and evoked (triggered) electromyography (EMG) can be utilized in combination with the above methods, providing a functional, three-dimensional assessment of the structural integrity of the pedicle (Isley et al. 2012). However, the spread of neuromonitoring has been delayed by its high costs, and by the finding that an intraoperative response to a neuromonitoring alert does not significantly reduce the rate of postoperative neurological deficit (Wiedemayer et al. 2002, Sanborn et al. 2012). In a cost-effectiveness comparison study, neuromonitoring was found to be the least cost-effective confirmatory technique for the placement of lumbar pedicle screws (Sanborn et al. 2012).

#### *2.2.1.1 Conventional methods*

Several approaches for the pedicle screw entry point in the lumbosacral spine have been used in the conventional freehand technique (Magerl 1984, Roy-Camille et al. 1986, Weinstein et al. 1988, Robertson et al. 1998, Karapinar et al. 2008, Miekisiak et al. 2015). A popular approach for the entry point is at the intersection of the horizontal midline of the transverse process and the vertical line tangential to the lateral border of the superior articular process in each lumbar vertebra (Magerl 1984). In the S1-vertebrae, the entry point is at the junction of the ala of sacrum and the superior articular process of S1.

Results of morphometric measurements of the lumbar transverse pedicle angles are presented in Table 2. Based on the measurement results, the schemes for the transverse angles of pedicle screw insertion begin from approximately 10–15 degrees at the L1, with 5-degree increments per level up to the L5 (Mattei et al. 2009, Pearson et al. 2017). In the sagittal plane, the direction of pedicle screws should be parallel to the superior endplate of the vertebra in the lumbar spine. At the S1, the direction of pedicle screws in the sagittal plane should be slightly ascending toward the superior endplate in order to reach the sacral promontory with the screw tip for bicortical grip, and in the coronal plane approximately 15–45 ° medially (Louis 1986, de Peretti et al. 1991).

Table 2 Examples of previous morphometric studies on the transverse lumbar pedicle angles.

| Reference | Level | Range (°) | Mean (°) |
|---|---|---|---|
| (Zindrick et al. 1987) | L1 | 6.5–14.5 | 10.9 |
| | L2 | 5.0–17.5 | 12.0 |
| | L3 | 8.0–23.5 | 14.4 |
| | L4 | 5.5–27.5 | 17.7 |
| | L5 | 19.0–44.0 | 29.8 |
| (Lien et al. 2007) | L1 | - | 8.5 |
| | L2 | - | 12.4 |
| | L3 | - | 15.3 |
| | L4 | - | 18.9 |
| | L5 | - | 24.4 |

After incision of soft tissues and exposure to the planned pedicle entrance point for a screw, the superior cortex of the pedicle entry site is removed, e.g. by a rongeur to reveal the cancellous isthmus of the pedicle (Karapinar et al. 2008). As a result, in the popular funnel technique, the cortical margins of the upper part of the pedicle act as a funnel to permit safe insertion of a pedicle probe through the pedicle isthmus along a low-resistance path (Gaines 2000, Viau et al. 2002).

The main screw insertion techniques are funnel, slide, and the in-out-in method, and the two main subsequent screw trajectories straightforward and anatomic (Perna et al. 2016). After the posterior pedicle entry site is first perforated with an awl, the probe is advanced, optionally with the assistance of x-ray or fluoroscopy, slowly and carefully. If any resistance is encountered, the probe is redirected. Thereafter, a pilot hole is prepared with a cannulated drill. Before the insertion of a screw, a ball-tipped feeler is used to verify that the circumferential bone all around the trajectory is intact (Karapinar et al. 2008). Also, the screws should be inserted relatively easily and should not be forced. Usually, anteroposterior and lateral x-rays or fluoroscopy are used to confirm the position of each screw (Miekisiak et al. 2015). In the laminoforaminotomy technique, a standard open laminoforaminotomy is performed prior to inserting a pedicle screw for each planned screw to get tactile feedback (Austin et al. 2002). Results of the previous studies of pedicle screw placement accuracy and complications are presented in Table 3.

Table 3 Previous studies where lumbosacral screws were placed with the aid of x-ray image intensifier or fluoroscopy excluding percutaneous cases, deformity corrections and trauma cases (NR: not reported, mos: months, pt: patient, w: with, op: operation, inst: instrumentation, Th: thoracic, L: lumbar, CSF: cerebrospinal fluid).

| Reference | Years | No of patients | No of screws | Detailed method | Follow-up time (mos) | Accuracy (%) | Region | Clinically relevant screw-related complications |
|---|---|---|---|---|---|---|---|---|
| (Saarenpää et al. 2017) | 1/2000–11/2010 | 147 | 837 | Biplanar fluoroscopy | 66 | 85.7 | Lumbosacral | 17 pts w only radicular pain, 5 pts w radicular pain and motor weakness, 1 pt w motor weakness; no revision |
| (Yu et al. 2017) | 1/2014–4/2015 | 401 | 1467 | Biplanar fluoroscopy | 4 | 74.7 | Lumbosacral | 3 pts w transient nerve root injuries, 9 pts w CSF leakage; no revision |
| (Ikeuchi et al. 2016) | 4/2008–7/2013 | 43 | 293 | Biplanar fluoroscopy | NR | 93.2 | Thoracolumbar | - |
| (Luther et al. 2015) | 2004–2010 | NR | 190 | Lateral fluoroscopy | NR | 87.4 | Lumbar | 22 pts required revision (8 pts w instrumentation failure, 8 pts w symptomatic progression, 6 pts w infection) |
| (Motiei-Langroudi et al. 2015) | 3/2012–12/2012 | 114 | 770 | Lateral fluoroscopy | NR | 97.7 | Thoracolumbosacral | 1 pt w radicular pain required revision, 4 pts w weakness, 3 pts w wound infection |
| (Shin et al. 2015) | 1–7/2010 | 20 | 138 | Lateral fluoroscopy | NR | 87.7 | Thoracolumbar | 2 pts w ipsilateral leg paraesthesia, one required re-operation (re-positioning of the screw) |
| (Koktekir et al. 2014) | 3/2004–9/2012 | 198 | 1218 | A) lateral, B) lateral +ap fluoroscopy | NR | A) 96.4, B) 98.8 | Thoracolumbosacral | A) 2 pts w radicular pain, 1 pt w radicular pain and motor weakness, 1 pt w motor weakness, 14 screws revised; B) 6 screws revised; all symptoms relieved w revision |
| (Nevzati et al. 2014) | 1/2007–5/2011 | 273 | 1236 | Biplanar fluoroscopy | NR | 80.0 | Thoracolumbosacral | 8 pts w radicular pain, 6 pts w radicular pain and motor deficit, 2 pts w radicular pain and sensory deficit; 28 screws revised |
| (Oh et al. 2013) | 1/2008–10/2010 | 126 | 558 | Biplanar fluoroscopy | 6 | 86.6 | Lumbosacral | 10 pts w radicular pain, 3 pts w motor weakness following revision within 2 days (weakness resolved completely over 3 months, but one had decreased sensation) |

| Reference | Years | No of patients | No of screws | Detailed method | Follow-up time (mos) | Accuracy (%) | Region | Clinically relevant screw-related complications |
|---|---|---|---|---|---|---|---|---|
| (Waschke et al. 2013) | 1995–2005 | NR | 1394 | Biplanar fluoroscopy | NR | 70.5 | Lumbosacral | 9 motor weakness |
| (Ringel et al. 2012) | NR | 30 | 152 | Biplanar fluoroscopy | NR | 68 | Lumbosacral | 1 pt w radicular pain required revision (re-positioning of the screw) |
| (Parker et al. 2011) | 6/2002–6/2009 | 964 | 6816 | Lateral radiograph | NR | 98.3 (Th: 97.5, L: 99.1) | Thoracolumbosacral | 8 pts had screw revision (3 pts w nerve root symptoms, 3 pts w infection, 1 pt w non-hardware-related symptoms, 1 pt because of prophylaxis against pseudoarthrosis), 45 pts w incidental durotomies and intraoperative CSF leak, 23 pts w surgical site infection, 14 pts w pulmonary emboli |
| (Silbermann et al. 2011) | 1–9/2009 | 30 | 152 | Biplanar C-arm | NR | 86.2 | Lumbosacral | 4 screws revised intraoperatively; 1 pt w radicular pain resolved by revision |
| (Amato et al. 2010) | 2/2003–6/2008 | 102 | 424 | Biplanar fluoroscopy | Minimum 8 | 95.0 | Lumbosacral | 2 pts w radicular pain and neurological deficit and 5 pts w only radicular pain (all recovered at follow-up), 2 pedicle fractures, 1 nerve root injury, 1 dural laceration, 5 postop anemia, 3 wound infections, 2 late hardware failure, 1 adjacent instability |
| (Merloz et al. 2007) | 1–10/2004 | 26 | 138 | NR | NR | 87.0 | Thoracolumbar | - |
| (Amiot et al. 2000) | 9/1994–12/1996 | 100 | 544 | Biplanar fluoroscopy | 6 | 84.7 | Thoracolumbosacral | 7 pts w motor or sensitive neurological deficits following re-operation; after 6 mos follow-up, 2 had no change in symptoms |
| (Laine et al. 2000) | 4/1998–6/1999 | 50 | 277 | Image intensifier | NR | 86.7 | Thoracolumbosacral | 2 pts w partial L5 nerve root lesion, 1 pt w major bleeding, 1 pt died 4 weeks later due to infection and cardiac arrhythmia, 1 had spinal area trauma and developed endplate fracture |

| Reference | Years | No of patients | No of screws | Detailed method | Follow-up time (mos) | Accuracy (%) | Region | Clinically relevant screw-related complications |
|---|---|---|---|---|---|---|---|---|
| (Lonstein et al. 1999) | 1/1984–12/1993 | 875 | 4790 | Biplanar fluoroscopy | 24–60 | 94.9 | Thoracolumbosacral | Pain after 222 ops required re-instrumentation, radicular pain/weakness after 9 ops required revision in 7 pts (in last follow-up 3 pts had residual weakness), 65 screws cut out and 36 re-inserted, 25 screws fractured (13 pts w pseudoarthrosis inst was re-inserted, in 3 pts inst was removed), 6 screws bent, 3 screws cased pedicle fracture (2 screws were removed), dural tear in 4 pts; evaluation postoperatively: plain radiography if no pain/neurological deficit |
| (Schulze et al. 1998) | 5/1992–4/1995 | 50 | 244 | Biplanar fluoroscopy | Minimum 9 | 59.0 | Thoracolumbosacral | 1 pt w radicular pain |
| (Laine et al. 1997) | 12/1994–4/1995 | 30 | 152 | Lateral fluoroscopy | NR | 78.9 | Lumbosacral | 1 pt w S1 nerve root irritation |
| (Castro et al. 1996) | NR | 30 | 131 | Biplanar fluoroscopy | NR | 60.2 | Lumbosacral | 1 pt w hypoesthesia disappeared w revision, 1 pt w motor weakness disappeared w revision; 1 pt w paraesthesia and 2 pts w motor weakness refused revision |

#### *2.2.1.2 Spinal navigation*

The limitations of extensive use of multiplanar x-ray or fluoroscopy in conventional spinal fusion surgery include the difficulty of using 2D-images for the real three-dimensional anatomy; suboptimal quality of the images, particularly in obese and/or osteoporotic patients; inability to configure axial plane images to direct screw placement; and high radiation exposure for the surgeon (Kalfas et al. 1995, Villavicencio et al. 2005). Due to the imaging shortcomings, the accuracy of pedicle screws placed with conventional fluoroscopy has been reported to be inferior to the navigated screws. In two systematic reviews and five large original papers comparing conventional fluoroscopy to navigation methods, the rate of accuracy of the screws being inside the pedicles in lumbar spine varied between 70.5 and 88.6 % for the non-navigated screws and between 86.8 and 98.9 % for the navigated screws (Amiot et al. 2000, Laine et al. 2000, Silbermann et al. 2011, Shin et al. 2012, Waschke et al. 2013, Mason et al. 2014, Luther et al. 2015). This is well in line with the clinical results of a large meta-analysis, in which the weighted mean accuracy of the screws in the lumbar spine was 87.3 % without navigation and 92.1 % with navigation (Kosmopoulos et al. 2007a). In a prospective randomized trial to compare radiation exposure for the surgeon during lumbar fusion between intraoperative imaging and navigation, and non-navigated freehand fluoroscopy groups, the accumulated radiation dose for the surgeon was significantly, up to 10.0 times, higher in the non-navigation group (Villard et al. 2014). Also, the radiation dose for the patient was higher with the freehand technique, but did not reach a statistically significant level (Villard et al. 2014). Today, for the above reasons, most surgeons utilize the aid of different navigation and intraoperative imaging modalities for the guidance of a screw placement.

Both optical and electromagnetic spinal navigation are based on the time of flight (TOF) principle, where the time of a light or electromagnetic wave traveling for a certain path length is accurately measured (Pycinski et al. 2016). Image-guidance requires that all components of the system are aligned and displayed in a single three-dimensional coordinate system. Thus, preceding the surgery, pre- or intraoperatively, the spinal anatomical volume of the patient is scanned, and the spinal image data are matched to the corresponding surgical anatomy. In a registration process, the matching algorithms process information to align a specific point in the image data to the corresponding spatial point in the surgical region by using real-time acquisition devices (Pycinski et al. 2016). The registration can be carried out by paired point registration, surface-based registra-

tion or automated registration. In paired point registration, totally at least three discrete anatomical points in the image data are aligned with the spinal anatomy. At least one point is matched at each level to be instrumented. After selection of a point in the image data, the navigation tool is placed on the corresponding point in the surgical field of the patient and the spatial position is calculated (Pycinski et al. 2016). Thus, the selected points in the image data are linked with the corresponding points in the patient. Slower surface-based registration means selecting several random points on the surface of the surgical field of the patient. No prior selection of points in the image data is needed. A map of the selected anatomy is then created and matched to the image data in the workstation (Tamura et al. 2005). Automatic registration requires intraoperatively acquired image data, and does not need any effort from the surgeon (Nottmeier et al. 2009). It needs reference frames attached both to the patient and to the imaging scanner. Both the paired point and surface-based registration algorithms can also be applied simultaneously to increase the accuracy of the matching process (Tjardes et al. 2010).

In optical tracking, at least two TOF-cameras apart from each other measure the depth of the three-dimensional scene ahead using the infrared (IR) light source and charge-coupled device (CCD) detectors (Pycinski et al. 2016). The IR-signal emitted by the IR source is reflected back from passive reflective spheres fixed in navigation tools, surgical instruments and a reference, to the CCD detectors. Each tool, instrument and reference must comprise at least three reflective spheres to be aligned in the three-dimensional space (Mezger et al. 2013). The spacing and positioning of the reflectors are programmed to the computer workstation, which then, using a navigation software, can calculate the exact location and direction of the tool and the anatomical point of the patient in the surgical field, based on the data of the CCD detectors.

At present, five navigation techniques can be distinguished. In 2D fluoroscopic navigation (1), lateral and anterior-posterior (AP) imaging is done immediately before the start of the procedure. The registration is performed automatically using reference frames. The navigation is then performed displaying these images on the workstation screen superimposed by a navigation tool for the screw entry point and trajectory (Resnick 2003, Rampersaud et al. 2007). Although the axial projection is not available, the radiation dose is much lower compared to conventional fluoroscopy. Intraoperative isocentric 3D fluoroscopic navigation (2) differs from the above in that the images are carried out by rotation of a special isocentric C-arm in a 180-degree arc around the patient. In this way, the acquired images can be reformatted to multiplanar images, including also the axial projection (Manbachi et al. 2014). Including all regions of the spine, a systematic review reported the rate of accurately placed screws to be

84.3 % and 95.5 % with 2D and 3D fluoroscopic navigation, respectively (Mason et al. 2014).

In CT-based navigation (3), the preoperatively scanned CT images are used without the need for intraoperative imaging. Registration is performed at each level, which is planned for instrumentation. During navigation, the surgeon is able to see the reformatted CT images in multiple planes superimposed by the navigation tool in real time (Schwarzenbach et al. 1997). In intraoperative CT navigation (4), a portable CT scanner (O-arm) is used to get a 360-degree sweep image around the patient during the operation (Scheufler et al. 2011) (Figure 3). The registration is carried out automatically with reference frames. This method provides reformatted images of a quality similar to those in conventional CT images, and hence is the most commonly used navigation technique at the moment in spine surgery. The intraoperative CT navigation has shown to be superior to the CT navigation based on preoperative images in the accuracy of pedicle screw position (Oertel et al. 2011, Costa et al. 2015, Liu et al. 2017). In a retrospective study of 9406 screws consisting mainly of degenerative pathologies as an indication of fusion in lumbar spine (74.4–79.7 %), the rates of accurately placed screws were 96.9 % and 98.6 % in the groups of preoperative and intraoperative CT scans, respectively (Costa et al. 2015). The advantages of intraoperative CT navigation over to CT navigation with preoperative scans are the acquisition of images in a surgical position, usually prone, and automatic registration, both of which reduce errors of navigation, since preoperative CT scans are invariably acquired in a supine position, and since manual registration is always a source of error (Oertel et al. 2011, Scheufler et al. 2011, Ling et al. 2014). The pitfalls that may be related to intraoperative CT navigation include inaccuracies in imaging and registration caused by the body warmer and movements of respiration, location of the reference arc far away from the entry point of a screw, changes in position of the patient during the operation, bending of instruments and movement of the reference arc after registration, all of which cause inaccuracy in the navigation (Rahmathulla et al. 2014, Rivkin et al. 2014).

In robotic navigation (5), a small robotic arm is placed on a frame attached to the spine of a patient. Automatic registration is based on matching of preoperative CT scans to intraoperative fluoroscopic images scanned when a fiducial array is placed on the frame (Roser et al. 2013). In navigation mode, the robotic arm moves into the appropriate position holding the surgical tool to guide screw insertion accurately along the suitable trajectory. In a randomized prospective study of a total of 148 screws comparing freehand technique, CT navigation with preoperative scans and robotic-assisted navigation in the thoracolumbar spine, the rates of accurately placed pedicle screws were 97.5 %, 91.7 %

and 98.6 %, respectively (Roser et al. 2013). The advantages of robotic surgery that have been mentioned: surgeon ergonomics, significant dexterity enhancement, reduction of radiation exposure for the patient and surgeon, excellent 3D visualization, capacity for repetitive motions and holding tools for long periods, possibility for percutaneous procedure, minimal paravertebral muscle dissection, minimal retraction and minimal risks for bleeding and infection (Devito et al. 2010, Roser et al. 2013). However, the robotic navigation is still under development, and the reported results of the accuracy of robotic navigation in pedicle screw positioning are so far unclear (Ringel et al. 2012, Marcus et al. 2014, Liu et al. 2016, Fan et al. 2017, Laudato et al. 2018).

Spinal navigation enhances orientation to the non-visualized spinal anatomy, which provides for the use of minimally invasive and percutaneous approaches (Mezger et al. 2013). In two retrospective studies using intraoperative CT navigation for altogether 495 percutaneously placed pedicle screws in the lumbar spine, the rates of accuracy of the screws being inside the pedicles were 97.0 % and 96.9 %, respectively (Houten et al. 2012, Kim et al. 2014). When comparing open and percutaneous intraoperative CT navigation approaches, the rate of superior facet joint violation was found to be significantly higher in open than in percutaneous technique, being 26.5 % and 4.0 %, respectively (Yson et al. 2013). In general, navigation techniques have been shown to significantly shorten the operation time (Rajasekaran et al. 2007, Sasso et al. 2007, Moses et al. 2013).

### *2.2.2 Radiological evaluation*

Due to the nearby located visceral, vascular and nervous structures, a reliable postoperative identification of misplaced pedicle screws is necessary. In postoperative assessment of the position of screws, several in vitro studies have reported unacceptably high rates of false-negative and/or false-positive ratings with AP and lateral plain radiographs in the lumbar spine (Weinstein et al. 1988, Ferrick et al. 1997, Learch et al. 2004, Choma et al. 2006, Brooks et al. 2007). In identifying a misplaced screw with plain radiographs of the lumbar spine, the sensitivity rate ranged between 31 and 94 % in the above-mentioned studies. Correspondingly, the specifity rate in identifying a correctly placed screw with radiographs varied between 13 and 90 %. The accuracy of plain radiographs to identify the screw position being inside or outside the pedicles, when compared with direct dissection and visualization, varied between 63 and 89 % in the studies where this was presented (Weinstein et al. 1988, Ferrick et al. 1997, Learch et al. 2004,

Brooks et al. 2007). Similarly, for CT scan assessment, the identified sensitivity, specifity and accuracy rates range between 67 and 94 %, 37 and 90 %, and 68 and 90 %, respectively (Yoo et al. 1997, Learch et al. 2004, Choma et al. 2006, Brooks et al. 2007). The change in the material of screws from CoCr alloy to titanium alloy considerably improved the sensitivity, specifity and accuracy, since the titanium screws produce fewer artefacts on radiographs and CT scan images (Yoo et al. 1997, Choma et al. 2006). Higher sensitivity, specifity and accuracy were also measured for a senior surgeon compared with a resident (Ferrick et al. 1997). Also, the use of a combination of radiographs and CT images improved the sensitivity, specifity and accuracy (Brooks et al. 2007). The addition of an oblique radiograph projection in the assessment did not improve any of the above parameters (Learch et al. 2004). When analysing each of the comparative studies separately, all the values of sensitivity, specifity and accuracy were higher with CT-based assessment than with plain radiographs (Learch et al. 2004, Choma et al. 2006, Brooks et al. 2007). The discrepancy between radiographs and CT has shown to be most striking with medially misplaced screws, where CT depicted ten times as many breaches of the pedicle than plain radiographs (Farber et al. 1995). Also, because of the better reproducibility of interpretation of CT images compared with plain radiographs, postoperative high-resolution thin-cut CT scans reconstructed in the axial, sagittal and coronal planes are the state-of-the-art method in accessing the position of pedicle screws (Weinstein et al. 1988, Castro et al. 1996, Kosmopoulos et al. 2007b, Ravi et al. 2011).

Different pedicle screw grading systems are used to measure the cortical breach of a pedicle by a screw in CT scans (Gertzbein et al. 1990, Castro et al. 1996, Odgers et al. 1996, Laine et al. 1997, Wiesner et al. 1999, Learch et al. 2004, Ravi et al. 2011, Miekisiak et al. 2015). The most commonly used method is the Gertzbein classification, where the cortical screw breaches are described by the extent of extra-cortical violation as: no evidence of cortical pedicle breach (grade 0), breach of less than 2 mm (grade 1), breach from 2 to 4 mm (grade 2), and breach of more than 4 mm (grade 3) (Gertzbein et al. 1990). In some reports, a breach of less than 2 mm is not considered to be incorrectly positioned, and it is included within the number of accurately placed screws (Amiot et al. 2000, Hodges et al. 2012, Mason et al. 2014). Additionally, some studies only count intraoperatively repositioned screws or the screws that caused complications postoperatively due to malposition (Mason et al. 2014). Separate systems for anterior vertebral body perforation have been generated (Ravi et al. 2011, Chiu et al. 2015, Miekisiak et al. 2015). In addition to breach extent, partly an in vitro study and finally a randomized controlled in vivo study added the direction to the assessment of breach (Castro et al. 1996, Laine et al. 2000). In general, screws

breached or lying inferiorly or medially in the pedicle have a greater chance of producing neurological symptoms (Gautschi et al. 2011). Different dimensions for safety zones of allowable encroachment to each direction have been proposed, but ultimately the virtual individual anatomy in question is conclusive (Karapinar et al. 2008, Mason et al. 2014). Therefore, there is no clear statement of different grades of a breach to well describe different probabilities of corresponding symptoms. Thus, the scoring systems are not surrogates of outcome measures, but should be regarded as tools (Gautschi et al. 2011).

### *2.2.3 Clinical outcome*

The evaluation of instrumented fusion should always include a clinical assessment in addition to an appraisal of screw position. In general, the outcome in terms of pain, disability and quality of life is carried out by using the same measures as described in section 2.1.6 for lumbar fusion. Additionally, a new neurological deficit or a new postoperative pain requires careful assessment of postoperative images to rule out conflict with a screw, in which case surgical revision is indicated (Gautschi et al. 2011). After the immediate recognition of a potentially fatal vascular injury, the need for replacement of a misplaced screw in close contact with a blood vessel is regarded as controversial (Gautschi et al. 2011).

However, a misplaced screw does not necessarily have clinical consequences. A minor breach of the pedicle wall can be asymptomatic, and the severity of the penetration is related to neurological deficit (Oh et al. 2013). Medial screw breaches are prone to cause dural tears, but breaches to all directions may cause symptoms related to nerve roots, particularly breaches to medial and, to a slightly lesser extent, to lateral directions (Lonstein et al. 1999, Nevzati et al. 2014). Additionally, lateral breaches can lead to vascular or visceral complications. In a review, clinically relevant complications related to screw misplacement were very rare and occurred in less than 0.5 % of all procedures (Gautschi et al. 2011). According to a meta-analysis of 4790 pedicle screws, only 0.2 % of them caused neurological symptoms with a breach rate of 5.1 % (Lonstein et al. 1999). The mean incidence of dural lesion has been reported to be 0.18 % per pedicle screw, and the estimated incidence of a clinically relevant dural lesion 0.16–0.41 % per patient of 5654 patients (Gautschi et al. 2011). Further, the incidence of irritation of a nerve root and other neurological complication, e.g. sensorimotor deficit, were reported to be 0.19 % and 0.04–3.24 % per pedicle screw, respectively (Lonstein et al. 1999, Gautschi et al. 2011). Resulting from a mis-

match between the screw size and the pedicle diameter, the overall pedicle breakage rate for lumbar fusion is reported to range between 0.2 and 2.7 % of the screws inserted (Faraj et al. 1997, Lonstein et al. 1999). The incidence of screw breakage mainly caused by metal fatigue is shown to range from 3 to 6 % of the screws inserted (Matsuzaki et al. 1990, Gautschi et al. 2011). Moreover, a misplaced screw may also lead to late spinal instability and screw pullout, which can also result from osteoporotic bone, excessive strain on the implant, uncorrected sagittal imbalance, torque of insertion and screw purchase. No significant difference between the pedicle screw placement technique used and the complication rate has been detected (Gelalis et al. 2012).

## 2.3 Bone grafting, bone graft substitutes and expanders

Emphasizing the vital importance of bone grafting for successful fusion, all spinal instrumentation eventually fails without solid bony fusion (Kalfas 2001). When treating degenerative conditions in the lumbosacral spine region with bone grafts, the constituent parts of the spine, like bone, muscles, tendons, other soft tissue elements, neural structures and vascular supply must be taken into consideration to achieve a successful clinical outcome (Fleming et al. 2000). The addition of bone graft also considerably changes the existing metabolic condition in the area of the surgery and in close proximity to it by launching a bone healing process, which has been described to be similar to the process occurring in fractured long bones (Boden et al. 1995). The objective of the bone grafting is formation of bone that becomes structurally integrated with the surrounding skeleton and provides the mechanical properties of load bearing and fatigue resistance necessary for durable and effective function (Fleming et al. 2000).

Bone is a dynamic biological tissue composed of metabolically active cells integrated into a rigid framework under a continuously occurring state of deposition, resorption and remodelling (Kalfas 2001). According to Wolff's law, bone adapts its external shape and internal structure in response to the mechanical forces it is required to support, which means that bone resorption may dominate without a sufficient load (Prendergast et al. 1995). The prerequisite of bone formation is the presence of a sufficient amount of osteogenic progenitors, capable of forming bone, distributed throughout the grafted volume (Fleming et al. 2000). An osteoconductive matrix is required to facilitate the attachment, migration and differentiation of osteoblastic progenitors with the adjacent skeleton. Also, a pluripotent population of osteogenic cells, still capable of differentiation along pathways leading to many tissue types, needs a stimulus, which allows

their progress to a bone phenotype (Fleming et al. 2000). In addition to signals from soluble growth factors secreted in autocrine or paracrine fashion, the 3D matrix with unique properties of porosity, degradation and chemical surface, may also secrete signalling molecules required to promote the osteoblastic differentiation to a bone phenotype. These signals strongly influence the quality and amount of tissue formation in a graft site (Fleming et al. 2000). Growth factors and adhesion molecules capable of influencing the cascade of osteoblastic differention are termed osteoinductive.

Additionally, bone formation still needs vascularity and mechanical stability, which are targets of a suitable surgical technique (Fleming et al. 2000). Meticulous preparation of a graft site ensures an adequate blood supply to deliver osteoblastic precursors and inflammatory cells secreting stimulatory factors, and careful tissue handling secures an optimal preservation of local osteogenic cells in the graft site. The mechanical environment in a graft site is an important biological stimulus, partly determining the differentiation pathway of cells, e.g. micromotion has been shown to direct connective tissue progenitors towards a fibrocartilaginous pathway, resulting in pseudoarthrosis (Fleming et al. 2000). Anyway, the presence of stress is required for bone formation (Prendergast et al. 1995).

Thereafter, the differentiated osteoblasts secrete an unmineralized organic matrix, which subsequently mineralizes to give the bone strength and rigidity (Kalfas 2001). As a consequence, osteoblasts became trapped within bone matrix, mature, and form osteocytes, which then control extracellular concentration of calcium and phosphorus, as well as adaptive remodelling of bone in paracrine fashion. Osteoclasts are responsible for resorption of bone, controlled by hormonal and cellular mechanisms. In addition to the cellular components, the bone tissue consists of approximately 10–20 weight-% water, with dry weight comprising about 70 % of inorganic components, primarily crystalline hydroxyapatite ($[Ca_3(PO_4)_2]_3Ca(OH)_2$), and 30 % organic components (Kalfas 2001, Feng 2009). Local factors and hormones, including parathyroid hormone, vitamin D and calcitonin heavily regulate bone metabolism (Kalfas 2001).

### *2.3.1 Autologous bone grafting*

Autologous bone graft from iliac crest remains the gold standard as the most effective graft material with its associated high fusion rates, and many modern graft options have been compared with it (Fischgrund et al. 1997, Fleming et al. 2000, Sengupta et al. 2006, Vaccaro et al. 2008a, Radcliff et al. 2012, Wojewnik

et al. 2014). Autologous bone graft is the only graft material presenting clearly all, osteogenic, osteoinductive and osteoconductive properties promoting bone formation and fusion. Due to its trabeculated nature, cancellous autograft has a large surface area lined with a population of osteoprogenitor cells and osteoblasts for osteogenesis, and acts mainly as an osteoconductive agent, supporting the ingrowth of new blood vessels and the infiltration of new osteoblasts precursors (Khan et al. 2005, Nandi et al. 2010). Resorption of cancellous autograft occurs after vascular ingrowth, and subsequent to arrival of osteoclasts. However, the cancellous autograft is unable to provide structural support, but integrates quickly and achieves a strength equivalent to cortical autograft within six to twelve months, and may also serve as a space filler (Nandi et al. 2010, Jakoi et al. 2015). By contrast, nonvascularized cortical autograft provides an immediate mechanical support and is used when structural integrity is the primary concern (Jakoi et al. 2015). Cortical autografts, however, become significantly weaker in mechanical strength during the initial six weeks after transplantation as a result of osteoclastic resorption and subsequent revascularization, but resorption gradually declines to normal levels at a year postoperatively (Stevenson 1999, Khan et al. 2005). The complete resorption of the graft with concomitant replacement with viable new bone begins at the graft-host interface proceeding to the mid-regions of the graft, and is called creeping substitution, describing the long process of the graft incorporation (Stevenson 1999, Fleming et al. 2000, Kalfas 2001, Khan et al. 2005). Autograft is usually harvested from local bone, including spinous processes, lamina and facets, and posterior and anterior iliac crest. The drawbacks associated with autografts include the limited volume of graft available, potential donor-site morbidity, increased operating time and blood loss (Coventry et al. 1972, Ubhi et al. 1984, Kurz et al. 1989, Younger et al. 1989, Goulet et al. 1997, Sawin et al. 1998, Kalfas 2001, Khan et al. 2005).

### *2.3.2 Allogenous bone grafting and demineralized bone matrix*

Allogenous bone graft avoids the complications associated with harvesting of autograft bone, and provides basically an unlimited volume of graft material with a wider selection of sizes and forms, e.g. gels, powders, fibres, pastes and chips, and structural properties than autograft bone (Fleming et al. 2000, Grabowski et al. 2013). Allograft is the bone transferred between genetically dissimilar individuals of the same species, screened, processed, sterilized and preserved for transplantation (Giannoudis et al. 2005, Kannan et al. 2015). As a result of processing to minimise the host's immune response, allografts lack viable cells to offer osteogenic properties, and are only weakly osteoinductive but more oste-

oconductive (Giannoudis et al. 2005). The more aggressive the allograft processing is, the fewer immunological responses occur. Therefore, fresh allografts are no longer used clinically. Of the processed allografts, frozen allografts induce stronger immune responses than freeze-dried allografts, but the frozen are more osteoinductive, better in mechanical properties and strength than the freeze-dried (Strong et al. 1996, Ehrler et al. 2000). Sterilization may further diminish osteoinductive properties (Stevenson 1999). With allografts, the time and resources needed for screening, sterile harvesting, transport, processing, sterilization, cutting, packing, quality control and distribution prior to transplantation are large (Fleming et al. 2000). The graft incorporation of allografts occurs by creeping substitution (Ehrler et al. 2000). Other disadvantages of allografts include the risk of disease transmission and potential bioincompatibility (Kannan et al. 2015). Due to inferior fusion results compared with autograft, allograft should always be used in combination with autograft or another osteoinductive agent in the lumbar spine (An et al. 1995).

Demineralized bone matrix (DBM) is the organic part of allograft bone, which is produced through decalcification from human cadaver bone by acid extraction (Grabowski et al. 2013, Kannan et al. 2015). DBM consists of collagen fibres (over 90 %) providing osteoconductivity, osteoinductive proteins including BMPs (only approximately 5 %), and other noncollagenous proteins (Lee et al. 2015). DBM is quickly revascularized, provides no structural strength, and is, hence, primarily used in a mechanically stable environment, and acts as suitable carrier for autologous bone marrow, with commercially available preparations of powders, granules, putties and strips (Nandi et al. 2010, Kadam et al. 2016). As the antigenic surface structure of bone is destroyed during demineralization, DBM does not evoke any appreciable local foreign body immunogenic reaction, but its disease transmission rates are similar to allograft (Nandi et al. 2010, Grabowski et al. 2013). The biological activity of DBM is presumably attributable to proteins and growth factors present in the extracellular matrix and made available by the demineralization process (Nandi et al. 2010). DBM is used as a bone graft expander rather than as a bone graft substitute (Giannoudis et al. 2005, Tilkeridis et al. 2014). In a prospective multicentre trial of 120 adult patients with instrumented lumbar PLF, iliac crest autograft was implanted on one side of the spine, and DBM (Grafton® DBM) and autograft composite on the contralateral side (Cammisa et al. 2004). At 24 months postoperatively, fusion rates of 52 % on the DBM side and 54 % on the iliac crest autograft side were determined according to plain and flexion-extension radiographs. In another prospective study of 73 patients with instrumented lumbosacral PLF, the fusion results of supplemental bone grafting with DBM putty enriched with bone marrow aspirate

(BMA), DBM putty combined with iliac crest autograft, and only autograft were compared (Vaccaro et al. 2007). At 24 months follow-up, fusion rates of 63 % in the DBM-BMA group, 70 % in the DBM-autograft group, and 67 % in the autograft group were found without significance using plain and flexion-extension radiographs. In a prospective multicentre randomized clinical trial of 41 patients with a single-level instrumented lumbar PLF, patients received either DBM (Grafton® DBM) with local bone or only iliac crest autograft (Kang et al. 2012). At 24 months' follow-up, fusion rates were 86 % for the DBM group and 92 % for the autograft group, when evaluated in flexion-extension radiographs and CT scans. As the physical function scores were higher in the DBM group, though not statistically significantly, fusion rates and clinical outcomes associated with DBM for lumbar fusion were considered to be comparable to the use of iliac crest autograft.

### *2.3.3 Bone morphogenic proteins*

Bone morphogenic proteins (BMPs) are osteoinductive soluble cytokines belonging to the transforming growth factor beta (TGF-β) superfamily of proteins (Wojewnik et al. 2014, Kadam et al. 2016). BMPs differ from other growth factors in that they can induce pluripotent mesenchymal cells to differentiate into bone- and cartilage-precursor cells, binding to and acting via serine-threonine kinase receptors on the surface of target cells, and then activating a host of intracellular signalling pathways (Reddi et al. 2009, Grabowski et al. 2013). Due to advances in molecular manufacturing methods, BMPs can nowadays be produced without immunogenic concerns. Absorbable collagen sponges (ACSs) are the most frequently used carriers for BMPs to maintain effective concentrations at the intended fusion sites (Kadam et al. 2016). Of more than twenty types of BMPs described, the US Food and Drug Administration (FDA) has approved the recombinant human (rh) form of BMP-2 as a component of a titanium cage for ALIF and for the repair of symptomatic, posterolateral lumbar spine pseudoarthrosis, and rhBMP-7 (also known as osteogenic protein-1 (OP-1)) for revision of lumbar PLF, where autograft and bone marrow harvest are not feasible or are not expected to promote fusion (Ong et al. 2010). The use of BMPs in primary PLF and TLIF of the lumbar spine is, hence, an off-label application.

In prospective, randomized and controlled comparative studies with instrumented lumbar PLF, rhBMP-2 delivered on a carrier had superior fusion rates varying between 86 and 100 % compared to autologous iliac crest bone graft with fusion rates between 40 and 89 % (Boden et al. 2002, Glassman et al. 2005,

Dimar et al. 2006, Dawson et al. 2009, Dimar et al. 2009, Hurlbert et al. 2013). While showing high fusion rates and good clinical outcomes, some of the above-mentioned studies have since been scrutinized due to initial underreporting of complications, potential conflicts of interest and the financial benefit that these authors gained from the conclusions in their study (Carragee et al. 2011, Kannan et al. 2015). Potential drawbacks of lumbar PLF with rhBMP-2 have been reported to be greater back and leg pain and inferior functional outcome during the early postoperative period, and higher rates of both epidural hematoma and wound complications (Carragee et al. 2011). In addition, high-dose rhBMP-2 has been shown to increase cancer rates (Carragee et al. 2011). In retrospective studies of altogether 893 interbody fusions with TLIF technique using a cage, rhBMP-2 and autograft, the rate of pseudoarthrosis was 0.9–4.8 % supporting the efficacy of rhBMP-2 for increasing reliable fusion rates (Mummaneni et al. 2004, Crandall et al. 2013). A retrospective cohort study and a review reported higher rates of complications, consisting of, e.g. postoperative radiculopathy, ectopic bone growth, radiculitis, subsidence, endplate resorption and osteolysis with the use of rhBMP-2 than without in PLIF and TLIF operations in the lumbar spine, concluding that rhBMP-2 may unnecessarily increase the risk of complications (Carragee et al. 2011, Adams et al. 2014). In three prospective, randomized and controlled studies comparing rhBMP-7 with autograft in lumbar PLF, all assessed fusion rates with rhBMP-7 were inferior to the fusion rates with autograft (Kanayama et al. 2006, Vaccaro et al. 2008a, Vaccaro et al. 2008b, Delawi et al. 2016). Thus, it was concluded that rhBMP-7 cannot be recommended in instrumented posterolateral lumbar fusion procedures (Delawi et al. 2016). Moreover, for the above reasons, the use of rhBMP-2 in fusions of the lumbar spine has decreased over the past few years (Kannan et al. 2015).

### *2.3.4 Tricalcium phosphate and hydroxyapatite ceramics*

Ceramics are synthetic scaffolds for bone growth that are biodegradable, feasible for large-scale production, easy to sterilize, nonimmunogenic and relatively nontoxic (Kannan et al. 2015). Due to their porous 3D structure, they are osteoconductive, but alone do not possess osteogenic or osteoinductive properties, and are mainly used as bone graft expanders in combination with autograft or BMA. The disadvantages of ceramics are their mechanical properties, brittleness and little shear strength, and hence they are used with rigid internal fixation until they are incorporated into host bone (Miyazaki et al. 2009). From a functional perspective, ceramics are classified into rapidly and slowly resorbing (Fleming et al. 2000). The most commonly used and extensively studied ceramics are tricalcium

phosphate (TCP) and hydroxyapatite (HA) of the calcium phosphate ($CaPO_4$) stoichiometry (Miyazaki et al. 2009). TCP is generally resorbed over months after implantation (Fleming et al. 2000, Spivak et al. 2001). Porous TCP is created by compacting TCP powder with a carrier, which is subsequently removed (Fleming et al. 2000). In commonly available TCP preparations, the porosity is approximately 35 %, with pores ranging between 100 and 300 μm. Porous TCP is removed from the implant site as bone grows into the scaffold (Giannoudis et al. 2005). A calcium- and phosphate-rich surface layer and local microenvironment characterize resorption of TCP. This surface layer with high calcium phosphate concentration enhances the integration of the implant into host bone, stimulating osteoclastic resorption, and consequently osteoblastic new bone formation within the resorbed implant (Fleming et al. 2000, Giannoudis et al. 2005). By contrast, commercially available HA is resorbed very slowly, if at all, under normal physiological conditions, the typical resorption rate being only 5–15 % per year (Fleming et al. 2000, Spivak et al. 2001). Thus, mechanically brittle HA is often modified and combined with other materials for improved functionality and faster resorption (Passuti et al. 1989, Giannoudis et al. 2005). HA has chemical similarity with the mineralized phase of bone accounting for osteoconductive potential and excellent biocompatibility, and has been established to be an excellent carrier of osteogenic cells and osteoinductive growth factors (Nandi et al. 2010). After incorporation, ceramic implant gradually acquires mechanical strength similar to cancellous spine (Giannoudis et al. 2005).

A prospective, randomized and controlled study of 62 patients with instrumented lumbar PLF compared results of β-form of TCP combined with local autograft, and iliac crest autograft combined with local autograft (Dai et al. 2008). At 36 months postoperatively, all operated levels were assessed as fused using plain and flexion-extension radiographs. In another prospective study of 61 patients with instrumented lumbar PLF, a hybrid graft of porous β-TCP /percutaneously harvested bone sticks/autologous BMA was placed on one side of the spine, and a local autograft on the contralateral side (Yamada et al. 2012). At 24 months' follow-up, fusion rates of 93.5 % in the hybrid group and 89.1 % in the local autograft group were assessed without significance using dynamic radiographs and CT. A prospective study of 42 patients with instrumented lumbar PLF made a comparison of local autograft on one side of the spine, and a mixture of local autograft and β-TCP on the contralateral side (Kong et al. 2013). The fusion rates were evaluated to be 57.1 % in the β-TCP group and 73.8 % in the local autograft group with plain radiographs, and CT at 12 months postoperatively. In a prospective trial of 34 patients with PLIF using β-TCP and BMA perfusion, the rate of pseudoarthrosis was defined as 38.6 % assessed with CT at 12

months after surgery (Thaler et al. 2013). Therefore, the authors of the two above-mentioned studies postulated avoiding the use of β-TCP.

With HA, a prospective, randomized and controlled study of 57 patients with lumbosacral PLF compared results of coralline HA, iliac crest autograft and both together (Korovessis et al. 2005). Radiological fusion was achieved in all operated levels in all groups using plain and flexion-extension radiographs and CT scans at one-year follow-up. Resorption of HA was found to be completed at one year postoperatively. However, the authors concluded that due to the small host bone area, HA is not appropriate for PLF use. In a prospective case-control study of 58 patients with instrumented lumbar PLF, results of implanted local autograft with iliac crest autograft, coralline HA with iliac crest autograft, and coralline HA with local autograft were compared to iliac crest autograft implanted on the contralateral side (Hsu et al. 2005). At 12 months' follow-up, using plain and flexion-extension radiographs, the fusion rates were 90.0 % in the local autograft - iliac crest autograft group, 78.9 % in the coralline HA - iliac crest autograft group, and 57.9 % in the coralline HA - local autograft group with a statistically significant difference between the first and last groups, when the fusion rate with iliac crest autograft only varied between 84.2 and 95.0 %. A retrospective study of 130 patients and 165 levels with PLIF made a comparison of the use of HA bone chip with local autograft, iliac crest autograft with local autograft, and local autograft only (Kim et al. 2012). Radiological fusion rates were 91.7 % in the HA group, 92.9 % in the iliac crest autograft group, and 94.6 % with local autograft only, when evaluated in plain radiographs at 12 months' postoperatively. Consequently, the evidence of the use of HA in fusions of the lumbar spine is conflicting.

### *2.3.5 Bioactive glasses*

Since Professor Larry Hench and co-workers discovered the first artificial materials to be capable of forming a chemical bond with bone, termed bioactive glasses (BAGs) in 1969, the research on BAGs has extensively expanded (Hench 2006). The original hypothesis of Professor Hench behind the choice of glass compositions was that as bone contains HA, if the implant material is able to form an HA layer in vivo, it may not be rejected by the body but bond directly with bone (Hench 2006). BAGs are synthetic, biocompatible and osteoconductive materials that have surface activity (Jones 2013). BAGs do not form an interfacial layer of fibrous tissue but instead form a living bond with the host tissues (Hench et al. 1972, Dusková et al. 2002, Hench 2006, Hench 2009). To be able to

interfacially bond to bone without toxicity effect, the proportions of the main components of BAGs ($SiO_2$, $Na_2O$, CaO, $P_2O_5$) must be within a certain narrow range (Wilson et al. 1981, Jones 2013).

Exposing the surface of BAG implant to extracellular fluids in living tissues, leads to release of biologically active silica and calcium ions, and subsequent activation of osteoprogenitor cells and rapid formation of a hydroxycarbonate apatite (HCA) layer for bonding with growing bone (Hench et al. 2004, Hench 2006, Hench 2009, Jones 2013). Instead of formation of a surface HCA layer, the key phenomenon is controlled rates of release of critical concentrations of soluble silica and calcium ions that lead to genetic up-regulation and activation of genes in osteoprogenitor cells (Hench 2006, Hench 2009, Jones 2013). Accumulation of dissolution products of BAG causes both the chemical composition and the pH of the solution to change, providing surface sites and a pH conductive to HCA nucleation (Jones 2013). The proposed reaction stages on the glass surface are (Hench et al. 2004, Jones 2013):

1. Formation of silanol bonds (Si-OH)
2. Release of soluble silica in the form of $Si(OH)_4$ to the solution
3. Condensation of Si-OH groups to form hydrated silica gel and repolymerization of the silica-rich layer
4. Migration of $Ca^{2+}$ and $PO_4^{3-}$ ions to the surface through the silica-rich layer to form an amorphous $CaO\text{-}P_2O_5$ on the top of silica-rich layer
5. Crystallization of the amorphous $CaO\text{-}P_2O_5$ layer to HCA

The formed biologically reactive HCA layer provides an ideal environment for adsorption of extracellular biological structures, and attachment, proliferation and differentiation of osteoprogenitor cells to form new bone that has a mechanically strong bond to the glass surface (Hench et al. 2002, Hench et al. 2004, Hench 2006). Glass composition has the greatest influence on the rate of HCA layer formation and bone bonding (Jones 2013). The gene expression of osteoprogenitor cells has been shown to be dose-dependent on the particular soluble silica and calcium ions mass concentration ranges, while the rate of bone bonding directly correlated with the activation energy of silica dissolution in the glass (Arcos et al. 2003, Hench 2009). In addition to osteoconductivity, BAGs are claimed to be osteostimulative through a direct control over genes that regulate cell cycle induction and progression toward a mature osteoblast phenotype (Vrouwenvelder et al. 1993, Oonishi et al. 2000, Xynos et al. 2001, Hench 2009).

Since the surface of BAGs has been shown to be resistant to cell-mediated degeneration, and since physicochemical degeneration is limited to the outer layer of BAGs, the initial phase of degeneration is mechanical, followed by the physicochemical phase (Wilson et al. 2006). As the above processes are slow, the degeneration of BAGs can take years (Lindfors et al. 2010b).

Because of their brittleness, conventional BAGs cannot share load with bone (Jones 2013). BAGs are traditionally processed by a melt-quenching route, producing dense glasses, as sol-gel-derived glasses tend to have an inherent nanoporosity, which can result in improved cellular response because of the nanotopography and a specific surface area of two orders of magnitude higher than for melt-derived glass with increased compressive strength (Sepulveda et al. 2001, Jones et al. 2006, Jones 2009, Arcos et al. 2010, Lei et al. 2010, Jones 2013). Ordered mesopores can enable, e.g. drugs to be stored within a mesophorous network and subsequently delivered (Brinker et al. 1999, Vallet-Regí et al. 2012). As designing a glass composition which can be sintered without crystallizing but which remains bioactive is a challenge, the sintering window has been widened by introducing network modifiers, e.g. $K_2O$, MgO to increase the activation energy for crystallization, and the compositional dependence of bioactivity has been modelled by the Na2O-K2O-MgO-CaO-B2O3-P2O5-SiO2 system (Brink et al. 1997, Hupa 2009). Borate-based BAGs have shown the ability to enhance new bone formation and have had controllable degradation rates closely matching the rate of new bone formation, while doping with trace quantities of elements such as copper, zinc and strontium has shown beneficial effects for healthy bone growth (Hoppe et al. 2011, Rahaman et al. 2011). Composite scaffolds can be produced of two or more types of materials, often polymers and bioactive ceramics, e.g. to achieve mechanical reinforcement (Rezwan et al. 2006, Fu et al. 2011, Vallittu et al. 2015).

#### *2.3.5.1 Chemical composition*

The main component of different melt-derived commercial BAG formulations is silica in oxide form ($SiO_2$), which establishes a tetrahedron network modified by oxides of metal ions (e.g. Na, K, Ca, Mg), which influence the properties of the glass (Strnad 1992, Hill et al. 2011) (Table 4). The melt-derived BAG formulations containing 45–52 weight-% of $SiO_2$ have been reported to achieve the most rapid bonding to bone; glasses with 55–60 weight-% of $SiO_2$ bond to bone at slower rates (Välimäki et al. 2006). BAGs containing greater than 60 weight-% of $SiO_2$ are bio-inert and do not bond (Hench 2006, Välimäki et al. 2006). In-

crease in the surface area of the glass by making a particulate or a nanoporous sol-gel-derived glass extends the bone bonding compositions to higher percentages of $SiO_2$ (up to 90 weight-%) in the glass (Hench 2006, Fiume et al. 2018). When the BAG composition exceeds 52 weight-% of $SiO_2$, the glass will bond to bone but not to soft tissues (Hench 2006). In the BAG S53P4 (Bonalive®), the putty-form differs from the granule-form by its synthetic binder component, consisting of 10 weigh-% of glycerol and 30 weight-% of polyethylene glycols (PEGs).

Table 4 Compositions of bioactive glasses 45S5 and S53P4 in weight-% (mol-%).

| Glass | $Na_2O$ | CaO | $P_2O_5$ | $SiO_2$ |
|---|---|---|---|---|
| 45S5 (Bioglass®) | 24.5 (24.4) | 24.5 (26.9) | 6.0 (2.6) | 45.0 (46.1) |
| S53P4 | 23.0 (22.7) | 20.0 (21.8) | 4.0 (1.7) | 53.0 (53.8) |

### *2.3.5.2 Antibacterial and angiogenetic properties*

A unique property of BAGs compared to all other graft materials is their ability to kill or inhibit the growth of a wide selection of bacterial species. Antibacterial effects of BAGs are linked with a rise in osmotic pressure in the vicinity of BAGs as a consequence of the leaching of ions from the glass surface, and a subsequent rise in pH as a result of rapid cation exchange of alkalies from the glass surface with $H^+$ and $H_3O^+$ in the solution (Stoor et al. 1998). In vitro, BAG S53P4 has been shown to be the most effective of the tested six BAG powders, having a bactericidal effect on 29 clinically important aerobic bacterial species (Munukka et al. 2008). In addition, two BAG powders and a sol-gel-derived material have shown a bactericidal or bacteriostatic effect on 17 clinically important anaerobic pathogens tested in vitro (Leppäranta et al. 2008). The antibacterial effect of BAGs has also been shown to increase with increasing pH and concentration of alkali ions, and hence with increased dissolution tendency of the glasses (Zhang et al. 2010).

Clinically, BAG S53P4 granules have shown successful outcome in the treatment of chronic osteomyelitis, as the rate of patients without recurrent infections ranged between 86 and 100 % in six studies of altogether 219 patients (Lindfors et al. 2010a, Drago et al. 2013, McAndrew et al. 2013, Romanò et al. 2014, van Gestel, et al. 2015, Ferrando et al. 2017, Malat et al. 2018). In vitro,

four tested clinically important bacteria, including methicillin-resistant Staphylococcus aureus were killed in contact with the granula- and powder-forms of BAG S53P4, but the reference materials TCP, inert glass and putty-form of BAG S53P4 did not show any antibacterial effect (Stoor et al. 2017). Nor has BAG 45S5 putty (Novabone Putty®) shown any antibacterial effect (Wren et al. 2010). In addition, different formulations of BAG S53P4 have shown favourable results in the treatment of multidrug-resistant strains and bacterial biofilm on prosthetic material in vitro (Drago et al. 2014, Drago et al. 2015). BAGs doped with various inorganic ions can also promote the antibacterial activity (Hoppe et al. 2013). $Ag^{+}$ ions can easily be introduced into a glass, and have demonstrated both bactericidal and bacteriostatic effects (Ahmed et al. 2006). The bactericidal properties are derived from the attachment of silver ions to bacteria DNA and RNA or to the tissue proteins leading to cell distortion (Rai et al. 2009). The antibacterial effects of gallium ions ($Ga^{3+}$) are due to disruption of bacterial Fe metabolism and interference with Fe signalling (Kaneko et al. 2007).

Since diffusion-dependent transport of oxygen and nutrients is limited to 100–200 micrometres from vessels, new vessels must be produced and penetrated into the porous scaffold of BAG to be able to form viable new bone (Lovett et al. 2009). In vitro, the dissolution products of BAGs have been demonstrated to stimulate fibroblasts to secrete angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), and to increase the proliferation of microvascular endothelial cells, inducing a significant increase in the formation of anastomosed networks of endothelial cell tubules (Day 2005). BAGs have also been shown to induce the mitogenic response in human endothelial cells, and the potential of BAGs to stimulate angiogenesis has been demonstrated to be related to the release of inorganic ions into the medium (Keshaw et al. 2005, Gorustovich et al. 2010, Zhao et al. 2015). Coating of VEGF-releasing polylactic-co-glycolic acid (PLGA) scaffold with BAG has been demonstrated to enhance angiogenesis and bone maturation in a critical-sized defect of rat cranium over three months (Leach et al. 2006). Further, the loading of collagen sponge with BAG has been shown to result in greater neovascularization and bone regeneration compared to sponge lacking BAG in an irradiated critical-sized rat calvarial defect (Leu et al. 2009). A recent strategy to enhance angiogenesis has been to design BAG scaffolds to trick the body into thinking that the bone defect site is hypoxic, resulting in inhibition of the hypoxia-inducible growth factor 1a (HIF-1a) degradation and the production of new blood vessels (Jones 2013).

#### *2.3.5.3 In vitro testing of bioactivity and biocompatibility*

In vitro testing of bioactivity is rapid and inexpensive; it avoids the complexity of interpreting various cell responses of in vivo studies, and ethical issues related to the use of animals (Huang et al. 1997). For bioactivity measurements, BAGs are usually immersed in buffer solution of simulated body fluid (SBF) or Tris (Tris hydroxymethylaminomethane and hydrochloric acid). Thereafter, the measurement of pH and analyses of ion concentrations of the immersion solution for formed surface reactions to BAG, and the examination of an HCA layer on the glass are performed (Kokubo et al. 2006, Zhang et al. 2008, Hupa 2009, Fagerlund et al. 2012, Varila et al. 2012). At present, microelectrodes are used for pH measurements in situ, and inductive coupled plasma (ICP) emission spectrometers for the ion analyses of the solution composition (Zhang et al. 2008, Fagerlund et al. 2012, Fagerlund et al. 2013). The analysis of the formed surface HCA layer can be carried out using scanning electron microscopy with an energy-dispersive X-ray analyser (SEM-EDXA), X-ray diffraction (XRD), high-resolution micro-computed tomography (μCT), Fourier transform infrared spectroscopy (FTIR), and other spectroscopic methods (Cerruti et al. 2005, Kokubo et al. 2006, Yue et al. 2011).

In addition to the above-described chemically defined bioactivity, biocompatibility is also required for a BAG to bond to bone. The changes in the local environment derived from BAG must be taken into account in order to assess the viability, proliferation and osteogenic differentiation of progenitor cells (Huang et al. 1997, Lei et al. 2010, Labbaf et al. 2011). In vitro cell cultures provide a simple and reliable method for testing biocompatibility, whose sensitivity has been proved to be equal to or greater than that of in vivo studies (Ignatius et al. 1996, Huang et al. 1997). Also, the presence of adverse cellular reactions can be assessed. Today, mesenchymal stem cells (MSC) of human or animal origin are widely used as a cell culture source because of their relative ease of isolation, rapid expansion in vitro and potential for pluripotent differentation into mesenchymal tissues (Haimi et al. 2009, Labbaf et al. 2011). Biocompatibility parameters can be evaluated by staining for fluorescence microscope, SEM, determining alkaline phosphatase activity, spectroscopic methods and the polymerase chain reaction (PCR) technique (Vrouwenvelder et al. 1994, Ignatius et al. 1996, Lei et al. 2010).

#### *2.3.5.4 Clinical studies of spinal fusion*

To date, only a few individual studies have been published on the use of BAGs in instrumented spine surgery. An apatite- and wollastonite($CaSiO_3$)-containg BAG-ceramic load-bearing spinal implant was placed in altogether thirty patients based on tumour, trauma and degenerative disease indications (Yamamuro et al. 1994). In an average of 14.9 months' follow-up studies, good bone formation was reported around the implant. In another study of 24 consecutive patients treated with lumbar PLF for degenerative indications, a stand-alone graft substitute of HA-BAG ceramic composite (Chitra-HABg) in the ratio of 80:20 of HA:BAG was placed on one side and an autograft on the contralateral side (Acharya et al. 2008). After approximately a minimum of one-year follow-up, 95 % of the Chitra-HABg levels had poor radiological consolidation and all autograft levels had excellent radiological outcome, although no statistically significant association of clinical outcome with the consolidation of the fusion mass was observed. The authors concluded that HA-BAG composites have no role as stand-alone bone graft substitutes in lumbar PLF. Ilharreborde and co-workers compared either iliac crest autograft alone or together with BAG 45S5 (Novabone®) as bone substitutes in the treatment of 88 consecutive patients with thoracic adolescent idiopathic scoliosis (Ilharreborde et al. 2008). At a minimum of two years' follow-up, no difference was observed between the groups in achieving fusion, but the loss of correction of the main thoracic curve was slightly less in BAG group. Both the complication rate and blood loss were lower within the BAG group, without reaching the statistically significant level.

In a prospective long-term follow-up study of 17 patients operated on a total of 41 levels with PLF for degenerative spondylolisthesis, BAG S53P4 granules were implanted alone on one side of the spine and an iliac crest autograft alone on the contralateral side (Frantzén et al. 2011). After eleven years postoperatively, radiological fusion was observed in 80.5 % of the treated levels in the BAG group and in 100.0 % of the levels in the autograft group, when assessed by CT scans. Compared to preoperative scores, the mean ODI score decreased by 57.1 %, the mean back pain on the VAS scale was reduced by 52.1 %, and the mean radicular pain decreased by 60.3 % during the eleven years' follow-up. The same arrangement of BAG S53P4 granules and autograft was used in another prospective long-term follow-up study of ten patients and 21 levels treated with lumbar PLF for an unstable lumbar burst fracture (Rantakokko et al. 2012). At ten years' follow-up, the CT-based radiological fusion had been achieved in 71.4 % of the fused levels in the BAG side and in 100.0 % of the levels in the autograft side, with the mean ODI score of 12 (range 0–46) and the mean pain score

for radicular and back pain of VAS 1 among all patients. The authors of the two last-mentioned studies concluded that the use of BAG as bone graft substitute in spinal fusion is safe, while a mixture of BAG and autograft could be even more efficient in achieving a solid bony fusion than BAG alone (Frantzén et al. 2011, Rantakokko et al. 2012). In a prospective and randomized study of 80 patients with one-level lumbar PLIF as degenerative indication, Lee and co-workers compared a $CaO\text{-}SiO_2\text{-}P_2O_5\text{-}B_2O_3$ BAG spacer with a titanium cage (Lee et al. 2016). At 12 months postoperatively, the radiological CT-based fusion rates were 89.7 % for the BAG spacer group and 91.2 % for the titanium cage group. The difference in fusion rates between the groups was not statistically significant, but the bone fusion area directly attached to the endplate was significantly greater in the BAG group. Both groups showed significant postoperative improvement in the ODI, SF-36, back and radicular pain scores without significant intergroup differences. Nor were significant differences between the groups observed in the extent of subsidence and osteolysis, or in adverse reactions as a whole.

## 2.4 Preclinical study models for spinal fusion

### *2.4.1 Animal models*

The use of animal models for assessing spinal fusion has been criticized due to the quadruped nature of the experimental animals, disparity in geometry of the lumbar spine, high fusion tendency in even-toed animals, and lack of possibility for long-term studies (Lee et al. 2004). In humans, the weight of the upper body acts on the lumbar spine which is not the case in quadrupeds. However, since stabilizing a horizontally aligned spine requires higher muscle forces and passive tension than stabilizing an almost balanced vertically aligned spine, the addition of axial loads directed to the lumbar spine may be even higher in large quadrupeds than in humans (Alini et al. 2008).

The New Zealand white rabbit is the most commonly used model for posterior and posterolateral lumbar fusion studies (Drespe et al. 2005, Cottrell et al. 2006). The progression from smaller to larger animal models is known as the process of establishing burden of proof, the last step of which for clinical studies is nonhuman primates, being obviously most closely related to humans based on size, upright posture and genetic make-up (Sandhu et al. 2002, Drespe et al. 2005). Lumbar vertebrae of sheep and goat are comparable in size to human vertebrae, making human spinal surgical techniques easily performed in them

(McLain et al. 2002). ROM of sheep spine in different directions has been found qualitatively similar in cranio-caudal directions to human spine (Wilke et al. 1997).

First, fusion of different bone graft substitutes and expanders can be evaluated, e.g. using the critical size defect (CSD) model, defined as the smallest size intra-osseous wound in a particular bone and species that will not heal spontaneously during the lifetime of the animal, or more precisely over the duration of the study (Schmitz et al. 1986, Vajgel et al. 2014). For instance, since unicortical critical size defect of an adult Copenhagen White rabbit tibia has been tested to be larger than 8 mm, it is generally not possible to create such a CSD in a New Zealand white rabbit tibia, because its anatomical size is smaller than the CSD (Aaboe et al. 1994).

### *2.4.2 Evaluation of fusion*

Experimental endpoints must be defined in advance, since many means of fusion assessment are only possible ex vivo. Of radiological modalities, μCT is more sensitive than regular CT, which again is more sensitive and specific than plain radiography; and quantitative CT can be used to quantify bone formation (Drespe et al. 2005). After euthanizing the animals and collecting the specimens, biomechanical testing can be performed by manual palpation for intervertebral motion, by more precise and quantitative pull-apart testing or multidirectional flexibility testing (Kanayama et al. 1999, Erulkar et al. 2001, Drespe et al. 2005). Histological analysis of decalcified or non-decalcified specimens with appropriate staining also enables the assessment of tissue characteristics, in addition to bridging bone, when passing out on the sectioned plane (Cheng et al. 2002, Drespe et al. 2005). Histomorphometric quantitative methods aid in quantifying the fusion mass (Kanayama et al. 1999, Cheng et al. 2002). The most recent method to evaluate fusion is a molecular technique of reverse transcription polymerase chain reaction by means of which the expression of different factors related to the fusion process can be assessed (Morone et al. 1998).

# 3 AIMS OF THE STUDY

The series of studies concentrated on evaluation of the critical factors in the surgical procedure of the lumbar spine fusion that influence the clinical results. At the same time, the preclinical assessment of the novel BAG S53P4 putty, and its clinical evaluation as bone graft expander for spinal applications were carried out. The following questions were originally addressed:

1) (I) Can the use of spinal navigation increase the pedicle screw position accuracy of even a single, very experienced senior neurosurgeon using conventional pedicle screw positioning methods for degenerative indications in the lumbosacral spine?

2) (II) Is the bioactive glass S53P4 putty bioactive and biocompatible in spite of its containing binder components in vivo?

3) (III) Does the bioactive glass S53P4 putty used as a bone graft expander together with autologous bone enhance fusion in clinical minimally invasive lumbosacral interbody fusion surgery?

4) (III) Does the bioactive glass S53P4 putty affect intervertebral cage subsidence in clinical minimally invasive lumbosacral interbody fusion surgery?

# 4 MATERIALS AND METHODS

## 4.1 Evaluating accuracy of pedicle screw positions in degenerative lumbar spine with open surgery

### *4.1.1 Patients and operations*

Patients between January 2000 and November 2010 with Nordic Classification of Surgical Procedures (NCSP) codes NAG62 and NAG63 were screened to find all patients with pedicle screw instrumented fusion in the lumbosacral spine, excluding the patients with the interbody fusion without pedicle screws. Only the patients whose primary indication for surgery was degenerative spondylolisthesis or spondylolysis et –olisthesis, but also some revision cases, were included. Of a total of 564 identified procedures, 147 were randomly selected for retrospective evaluation of pedicle screw position. The number of screws inserted in the operations ranged between four to twelve, six screws being the most common number, inserted in 46.3 % of the patients. Altogether, the data consist of 837 pedicle screws.

### *4.1.2 Surgical procedure*

All operations were carried out by the same, very experienced neurosurgeon (E. K.), who had performed approximately 500 lumbosacral fusions before the beginning of the series. The procedure was started with decompression, followed by insertion of the screws first on the left side of the spine and then on the right side. The fixation of the rods and preparation of the posterolateral fusion bed were performed last.

The bony cortex at the screw insertion site was perforated with an awl, and the screw channel was prepared first with a blunt pedicle probe and thereafter with a drill. A thin pedicle feeler was used to verify that the cortex was intact. In the lumbar spine 5.0 and 6.0 mm, and in the sacral spine 7.0 mm polyaxial Legacy® (Medronic, Memphis, TN, USA) or Pangea® (DePuy Synthes, Oberdorf, Switzerland) screws were used. The pedicle preparation was carried out and the pedicle screws inserted according to anatomical landmarks supported by AP and lateral plain radiographs. At the end of operation, screw positions were veri-

fied with AP and lateral radiographs. The surgical technique remained unchanged over the study series.

### *4.1.3 Radiological evaluation*

Postoperatively, the screw positions were evaluated by a CT protocol with transaxial images of the instrumented vertebrae level and serial cuts through each pedicle perpendicular to its longitudinal axis. Thus, a helical CT was performed using either a Siemens Somatom Volume Zoom 4-slice CT, or a Siemens Somatom Sensation 64-slice CT (Siemens AG Healthcare Sector, Erlangen, Germany). The image data were reconstructed to 3.0 mm axial, coronal, and sagittal slices. During the study series, the routine verification of screw positions was performed for all operated patients within three postoperative days.

Thereafter, two independent spine surgeons assessed the images: one neurosurgeon (J. F., later: surgeon 1) and one orthopaedic surgeon (T. L., later: surgeon 2). An independent neuroradiologist (J. H.) evaluated 12.9 % of the patients. The pedicle screw position was graded as: inside the pedicle, or perforation of the bony pedicle cortex up to 2 mm, from 2 to 4 mm, from 4 to 6 mm, or more than 6 mm. The direction of the breach was graded at 90 ° intervals as medial, inferior, lateral or superior (Figure 4).

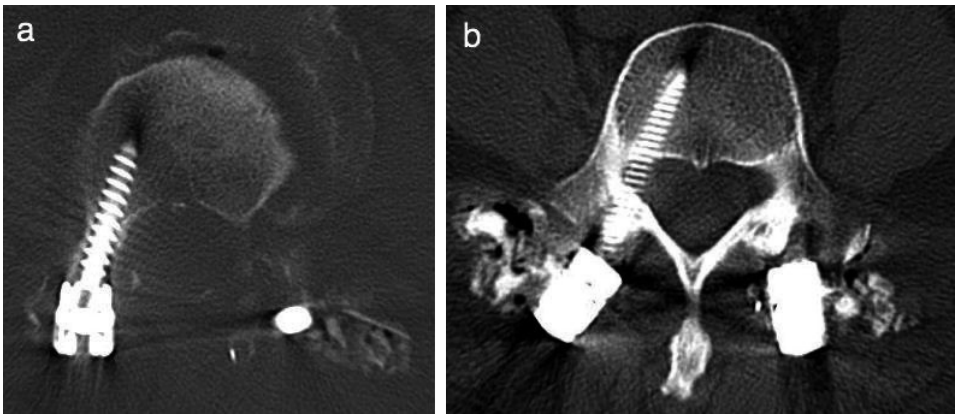


Figure 4 (a) Both surgeons evaluated the right L4 pedicle screw to be within the bony pedicle cortex in a patient with remarkable scoliosis in the coronal plane, in the lumbar CT at two days postoperative. (b) Both surgeons assessed the right L4 pedicle screw to breach the pedicle 4–6 mm medially in the lumbar CT on the first postoperative day.

### *4.1.4 Clinical evaluation*

In addition to immediate postoperative evaluation during the hospital stay, all operated patients were admitted to routine follow-up in the outpatient clinic at three months and at one year postoperatively. Thereafter, postoperative symptoms up to a minimum of 5 years and 6 months were retrospectively evaluated from the patient records concerned of the patients with pedicle breaches.

### *4.1.5 Statistical methods*

Statistical analyses were carried out using SAS system for Windows, version 9.4 (SAS Institute Inc, Cary, NC, USA), and SPSS system for Mac, version 24 (IBM Corp., Armonk, NY, USA). Percentages and frequencies were used to describe the data. The differences in categorical variables were tested using Pearson's chi-squared test, and Cohen's kappa coefficient (K) with 95 % confidence interval (95 % CI) measured the agreement between two observers at a time in grading the position of pedicle screws, similarly as in earlier studies (Kosmopoulos et al. 2007b, Dakhil-Jerew et al. 2009, Ravi et al. 2011). In complete agreement between the observers, $\kappa = 1$. If the agreement among the observers was very poor (worse than chance), $\kappa \leq 0$. Kappa ranges were defined as slight ($0.00 \leq K \leq 0.20$), fair ($0.21 \leq K \leq 0.40$), moderate ($0.41 \leq K \leq 0.60$), substantial ($0.61 \leq K \leq 0.80$), and almost perfect ($0.81 \leq K \leq 1.00$) agreement (Landis et al. 1977). P-values less than 0.05 were considered statistically significant.

## 4.2 Biocompatibility and performance of bioactive glass S53P4 putty compared to granules in rabbit model

### *4.2.1 Ethical approval of the animal experiments*

The study was performed in a laboratory accredited by The Association for Assessment and Accreditation of Laboratory Animal Care International in accordance with the Swiss Federal Act on Animal Protection under the license number 409/2010. All applicable international, national, and/or institutional guidelines for the care and use of animals were strictly followed.

### *4.2.2 Composition, manufacturing and properties of bioactive glass S53P4 putty*

BAG S53P4 putty consists of osteostimulative $CaO\text{-}P_2O_5\text{-}Na_2O\text{-}SiO_2$ BAG S53P4 granules (size 0.5–0.8 mm, 48 weight-%) mixed with spherical (BAG S53P4) granules (size 0.09–0.425 mm, 12 weight-%) and a synthetic binder (mix of glycerol and three chain lengths of PEG, 40 weight-%). The composition of the bioactive glass granules of BAG S53P4 putty is (by weight-%): $SiO_2$ 53 %, $Na_2O$ 23 %, CaO 20 % and $P_2O_5$ 4 %. In the chemical composition, the putty-form of BAG S53P4 differs from the granule-form by its synthetic binder.

During the manufacturing of BAG granules, the raw materials are melted in crucibles for three hours at 1360 ºC, casted and then annealed at 520 °C for an hour before cooling to room temperature overnight in an electric furnace. Thereafter, the glasses are crushed and remelted for homogeneity. For manufacturing of BAG putty, the synthetic binder (mix of glycerol and PEGs) and the BAG granules are again melt-mixed together to a paste-like product.

Based on the BAG S53P4 granules, BAG S53P4 putty is a synthetic, bioactive, osteoconductive and osteostimulative paste-like bone void filler that is easy to handle and implant. The binder fixes the granules temporarily together. The granules and the binder are provided as a premixed extrudable, pliable cohesive material, packed in a syringe-like applicator and sterilized by gamma irradiation.

### *4.2.3 Study design*

A prospective, in vivo comparison study of putty- and granule-forms of BAG S53P4 was performed to investigate the biocompatibility and bioactivity of BAG S53P4 putty, and to exclude its local and systematic harmful effects and toxicity. Two cavital non-CSDs were created in both proximal tibial bones of twenty-eight New Zealand white rabbits, and all four defects of the same animal were filled with the same implant, either putty- or granule-form of BAG S53P4. The animals were followed for clinical signs, food consumption and body weight post-operatively, and blood and urine were sampled for clinical laboratory investigations at four or eight weeks post-implantation. After the termination of animals either at four or eight weeks post-implantation, the animals were necropsied, and selected specimens were weighed, histologically processed and assessed.

### *4.2.4 Surgical procedure*

For creating the cavital defects in the tibial bones, twenty-eight male and female New Zealand white rabbits were anaesthetized, the back legs of the animals were shaven, and the area of the incision was cleaned with a standard disinfection solution of Betadine. An incision was made in the skin directly above the tibia of each leg and the proximal tibial area was isolated. Two holes (diameter of 2 mm and depth of 6 mm) were drilled per tibia using a water-cooled drill (penetrating through the cortex into the cancellous bone area), 8–10 mm apart from each other. The periosteum was destroyed during the drilling. The holes were filled with either the BAG S53P4 putty or with the control BAG S53P4 granules (0.5–0.8 mm in size) using a sterile instrument (e.g. a thin spatula). Special attention was paid to filling the holes completely with the test or the control implant. Finally, the wound was closed with sutures, which were removed approximately ten days postoperatively. An experienced surgeon performed all implantations.

### *4.2.5 Sampling*

The tissue specimens for histopathology were collected from each tibia so that both implanted holes were included as a whole, and forwarded for histological analyses. Each tibial sample was fixed in 10 % buffered formalin solution and reduced in size so that each block contained one implanted hole. These small samples were dehydrated in growing alcohol series and embedded in methyl methacrylate (MMA). The cutting-grinding technique was used after polymerization to produce thin, 80–100 μm sections. The plane of sectioning was directed along the long axis of the implanted hole. Thereafter, the histological sections were stained with Paragon stain and evaluated in a light microscope. Representative images were taken with both low magnification (to show the whole implanted holes) and high magnification (to show details).

### *4.2.6 Histopathological analysis*

Structural changes in BAG material, tissue integration, bone formation, level of vascularization, growth of the periosteum, and biocompatibility of the BAG S53P4 putty and granules were assessed from each tibial histological bone tissue sample. The test items were compared to the controls to find out whether the synthetic binder had any effects on the performance of the granules and on the formation of new bone. In addition, the filling volume of the granules in the defect

was assessed after the binder was diluted away, during the specimen preparation. Special attention was paid to osteogenesis, occurrence of connective tissue, the amount of new bone, and structural changes in the remaining test or control materials.

The histological gradings were defined to the current situation in every case of histological change (Morton et al. 2006, The International Organization for Standardization 2009). Incidence of cortical, intramedullary and periosteal granules, and spheres in the BAG S53P4 putty group, were estimated as present, not present, and not assessable. Structural changes in the granules and spheres (in the BAG S53P4 putty group) were graded on a four-step scale as (0) no structural change, (1) < 40 % of granules/spheres shrunken, (2) 40–70 % shrunken and (3) > 70 % shrunken. In addition, integration of granules/spheres in the formed bone tissue was scored on a four-step scale as (0) no integration, (1) < 40 %, (2) 40–70 % and (3) > 70 % of the surface of granules/spheres in the defect surrounded by the new bone. The filling volume, i.e. the percentage of the volume of the defect filled by the implants and new bone was graded as (0) none, (1) < 40 %, (2) 40–70 % and (3) > 70 %. Further, cortical ossification was graded on a six-step scale as (0) no new bone formation; (1) new bone formation around the implants; (2) new bone formation around the implants and at margins of the drilled hole; (3) new bone formation around the implants and at the margins of drilled hole including proximal inner and outer tibial bone borders with presence of thin bridging bone trabeculae; (4) medium–large bone trabeculae bridging the whole defect and the surrounding implants, slight new bone formation extending along inner and outer tibial bone borders; and (5) large bone trabeculae bridging the whole defect and the surrounding implants, prominent new bone formation extending along inner and outer tibial bone borders. Intramedullary ossification was graded on a five-step scale as (0) with no new bone formation, (1) with thin new bone formation around the implants covering less than 50 % of the granules surface, (2) when covering more than 50 % of the granules surface, (3) with new bone formation around the implants along with bone trabeculae, and (4) with bridging the bone trabeculae. Stromal cell reaction was scored as (0) non-existent, and (1) slight, (2) moderate or (3) marked sheet of fibres and cells around the implants. Periosteal growth over the defect was scored as (0) non-existent, (1) slight fibrosis, (2) moderate fibrosis and (3) marked fibrosis. Finally, vascularization in the defect was graded as (0) non-existent, (1) few blood vessels, (2) moderate blood vessels, and (3) many blood vessels.

### *4.2.7 Statistical methods*

Statistical analyses were performed using SPSS system for Mac, version 24 (IBM Corp., Armonk, NY, USA). The collected data were described using absolute and relative values. The normal distribution of the body weights, the clinical laboratory data and the gradings of microscopic findings was first tested visually from calculated histograms and secondly by the Shapiro-Wilk test. Consequently, the normally distributed test and control values were analysed by the parametric two-sample Student's t-test. If the values could not be assumed to follow a normal distribution, the non-parametric Mann-Whitney U-test was used for analysis. P-values less than 0.05 were considered statistically significant.

## 4.3 Bioactive glass S53P4 putty as bone graft expander in minimally invasive lumbosacral fusion

### *4.3.1 Patients*

Patients between January 2013 and December 2016 with NCSP codes NAG62, NAG63 and NAG66 were screened to find all patients operated on MI-TLIF in the lumbosacral spine with BAG S53P4 putty (BonAlive® putty; BonAlive Biomaterials Ltd., Turku, Finland) as bone graft expander. The primary indication for surgery in all patients was degenerative lumbosacral disease, but also revision cases after previous lumbosacral decompression were included. As a result of screening, a total of 21 procedures for 21 patients were identified. However, one of the 21 patients died from an acute myocardial infarction nine days after the operation. The remaining thirteen female and seven men were operated on 24 lumbosacral levels with interbody fusions in the Department of Neurosurgery at Turku University Hospital between September 2014 and November 2016. The enrolled patients had undergone unsuccessful conservative treatment of degenerative and/or postoperative back pain and/or radicular symptoms for at least a year before they were operated. The mean age of the patients included was 49.3 years, and five of them had previously undergone decompressive lumbosacral surgery.

### *4.3.2 Surgical procedure*

One neurosurgeon (J. F.) operated on all patients. Four patients were operated for a two-level and sixteen patients for a single level MI-TLIF. A total of 24 MI-

TLIF levels were operated in twenty patients. The most common operated level was L5/S1 (50.0 % of the operated levels). All procedures were performed percutaneously on one side, and through a Wiltse´s approach on the symptomatic side. A navigation reference was first fixed with a clamp to the iliac crest. Then, cannulated Viper® MIS extended tab screws (DePuy Synthes, Le Locle, Switzerland) or, in one case, Everest® MIS screws (K2M, Leesbury, VA, USA) were inserted percutaneously using spinal navigation based on intraoperative 3D imaging (StealthStation® S7® Navigation System and O-arm® Imaging System, Medtronic Navigation, Louisville, CO, USA). Thereafter, a contralateral Wiltse's approach was used. Subsequent to inserting the cannulated screws, facetectomy and discectomy were performed. Endplates were prepared and the fusion beds of the PEEK InterFuse® T-cage modules (VTI, Minneapolis, MN, USA) were filled with the mixture of BAG S53P4 putty and autograft chips (Figure 5). After packing the mixture of BAG S53P4 putty and autograft chips in the anterior disc space, and implanting the cage, the rods were inserted, compression was applied and the set screws were tightened on both sides. Intraoperative 3D control imaging was conducted, and a mixture of BAG S53P4 putty and autograft chips was implanted on the transverse processes of the symptomatic side after decorticating to bleeding bone, before the multilayer closure.

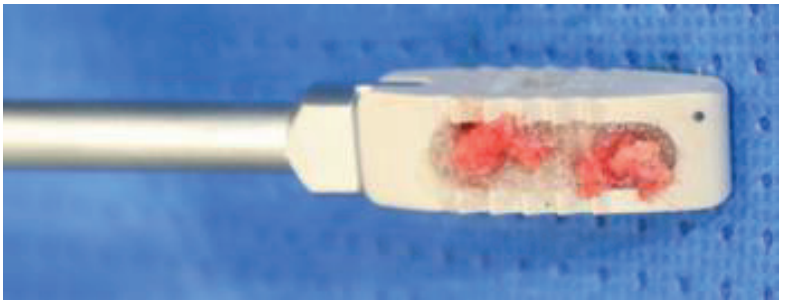

Figure 5 A module of the InterFuse® T-cage packed with a mixture of BAG S53P4 putty and autograft chips prior to implanting.

### *4.3.3 Radiological evaluation*

All operated patients have undergone routine preoperative lumbosacral spine MRI and flexion-extension radiographs. Intraoperatively, a 3D flat panel scan was performed in order to verify the correct position of the implants. Static plain radiographs were performed immediately postoperatively, when ambulatory, and

at three, twelve and 24 months postoperatively. When patients had specific complaints, they were further investigated with CT with or without MRI scans.

An independent neuroradiologist (J. H.) estimated resorption of the mixture of BAG S53P4 putty and autograft by plain lumbar spine radiography on a three-step scale (Table 6). In grade 1, the columns of the mixture of BAG S53P4 putty and autograft were still distinguishable, while in grade 2 only partly distinguishable, and in grade 3 not at all distinguishable. Correspondingly, interbody fusion was defined as presence of intervertebral bridging bone, without having had a revision or evidence of instrumentation loosening and/or breakage on the CT studies (Isaacs et al. 2016). The same independent neuroradiologist assessed bridging bone on a four-step grading scale including criteria about biological material incorporation and remodelling, and presence of lucency around the cage, in addition to the presence of bridging bone (Kumar et al. 1993). The levels meeting the criteria of grades I or II were considered as bridged, whereas grades III and IV were judged not bridged. Furthermore, fusion of the posterolateral implants was assessed according to the four-step Bridwell fusion grading system primarily from CTs, and if not available, from plain radiographs (Bridwell et al. 1995). The disc height was evaluated from available preoperative and postoperative images.

### *4.3.4 Clinical evaluation*

The routine clinical follow-up visits in the outpatient clinic were programmed at three and twelve months postoperatively, while the 24 months' follow-up was merely a personal telephone interview. The minimum follow-up time was twelve months. The clinical outcome was measured as presence of low back pain, radicular leg pain, motor deficit, paresthesia and instability symptoms, and according to Odom's criteria, as excellent, good, fair or poor (Odom et al. 1958). In the lumbosacral spine, excellent outcome was adapted to mean that all preoperative symptoms were relieved and pain reduced, whereas good outcome was defined as minimal persistence of preoperative symptoms and unchanged or improved preoperative abnormal findings, fair as definite relief of some preoperative symptoms when other symptoms were unchanged or slightly improved, and poor as worse or unchanged signs and symptoms (Mobbs et al. 2014).

### *4.3.5 Statistical methods*

Statistical analyses were performed using SPSS system for Mac, version 24 (IBM Corp., Armonk, NY, USA). Differences in resorption grades between two time points at a time were tested using the test of symmetry. The non-parametric Wilcoxon signed-rank test was used to measure the differences in disc heights before and after the operation. P-values less than 0.05 were considered statistically significant.

# 5 RESULTS

## 5.1 Accuracy of pedicle screw position in degenerative lumbar spine with open surgery

### *5.1.1 Pedicle perforation rate, direction and magnitude*

According to the radiological assessment of surgeons 1 and 2, the pedicle screws were inside the pedicle in 84.8 % (710/837) and in 86.6 % (725/837) of the screws, respectively. Of the patients, 48.3 % and 53.7 % were graded to have all the screws inside the pedicles according to surgeons 1 and 2, respectively. Surgeon 1 evaluated that 70.9 % and surgeon 2 that 69.6 % of the breached screws, respectively, breached to the clinically most important directions, either medially or inferiorly. According to both surgeons, the screw breach occurred more often on the left than on the right side pedicles ($p = 0.02$ and 0.03) in medial and inferior directions.

Pedicle breaches up to 2 mm were detected in 11.6 % and in 10.3 % of the screws according to surgeons 1 and 2, respectively. Surgeons 1 and 2 graded that at least 4 mm breached 3.6 % and 3.1 %, and more than 6 mm 1.9 % and 1.8 % of the screws, respectively. Totally, fourteen patients were assessed to have a single or multiple pedicle breach of at least 4 mm by either of the surgeons, and in ten of these patients screws directed either medially or inferiorly. Furthermore, eight patients were evaluated to have a pedicle breach of at least 6 mm, and in six of eight patients breaches were directed either medially or inferiorly. Between the assessments of the two surgeons, the pedicle breach was evaluated to differ over 2 mm only in five screws (0.6 %).

Most of the breaches occurred in the L5 level, where surgeons 1 and 2 graded pedicle breach in 20.7 % and in 16.1 % of the screws, followed by the L4 level with 14.7 % and 15.4 % of the screws, respectively. The fewest breaches were detected in the S1 level, where surgeons 1 and 2 found pedicle breach only in 9.4 % and in 7.1 % of the screws, respectively.

### *5.1.2 Correspondence of pedicle perforations with reported clinical symptoms*

On the site corresponding to the breach, new postoperative radicular pain and/or sensorimotor weakness was detected in 25.6 % and in 26.1 % of patients with pedicle breach evaluated by the surgeons 1 and 2, respectively. Nevertheless, no early revision was performed for screw misplacement. Of the patients with neurological symptoms corresponding to screw perforation site, 95.0 % and 83.3 % had assessed screw breach either medially or inferiorly by surgeons 1 and 2, respectively. Nine of ten and five of six patients with a pedicle perforation of at least 4 mm and at least 6 mm, respectively, either medially or inferiorly had postoperative neurological symptoms corresponding to the breach (Table 5). One patient graded to have a medial pedicle breach of ≥ 6 mm by only one of the surgeons, did not have breach-related symptoms. None with pedicle breach of at least 4 mm in the superior or lateral directions had postoperative breach-related neurological symptoms.

### *5.1.3 Interobserver agreement*

Most of the screws (63.0 %) were inserted in either L4 or L5 levels. At these levels, the inter-observer agreement between the surgeons was mostly substantial ($0.61 \leq K \leq 0.80$), and at minimum moderate ($K \geq 0.53$) in spatial location and direction. Between the surgeons and neuroradiologist, however, the inter-observer agreement strength varied considerably, from slight to almost perfect ($K = 0.02–0.81$) in spatial location and direction.

Table 5 Patients assessed to have pedicle breach of at least 4 mm with direction, magnitude, number of evaluators detected, level, side and new postoperative symptoms.

| Patient | Direction | Magnitude (mm) | Number of evaluators | Level | Side | New postoperative symptoms |
|---|---|---|---|---|---|---|
| 1 | Medial | 4–6 | 1 | L5 | dx. | Radicular pain on the right |
| 2 | Medial | 4–6 | 1 | L5 | dx. | Radicular pain and numbness on the right |
| 3 | Medial,<br>Medial<br>Medial,<br>Medial | > 6, 4–6<br>4–6, 4–6 | 2 | L5<br>L5 | dx.,<br>sin.<br>dx.,<br>sin. | None |
| 4 | Medial<br>Superior,<br>Medial | 4–6<br>4–6, > 6 | 2 | L4<br>L4 | sin.<br>dx.,<br>sin. | Radicular pain on the left buttock |
| 5 | Medial<br>Medial | 4–6<br>4–6 | 2 | L4<br>L4 | dx.<br>dx. | Radicular pain on the right |
| 6 | Superior<br>Superior | 4–6<br>4–6 | 2 | L4<br>L4 | dx.<br>dx. | None |
| 7 | Superior,<br>Lateral<br>Superior | 4–6, > 6<br>4–6 | 2 | L4,<br>L5<br>L4 | dx.<br>dx. | None |
| 8 | Medial,<br>Medial<br>Inferior | 4–6 , > 6<br>> 6 | 2 | S1<br>S1 | dx.,<br>sin.<br>sin. | Radicular pain on the left, in ENMG new light left nerve root injury (S1) on the left and new moderate nerve root injury (L5) on the left |
| 9 | Inferior<br>Inferior | > 6<br>4–6 | 2 | L5<br>L5 | dx.<br>dx. | Radicular pain (L5) on the right and new sensomotor deficit (L5) on the right |
| 10 | Inferior | 4–6 | 1 | L5 | dx. | Radicular pain on the right |
| 11 | Superior | 4–6 | 1 | S1 | dx. | None |
| 12 | Inferior<br>Medial | > 6<br>> 6 | 2 | S1<br>S1 | sin.<br>sin. | Foot numbness (S1) on the left |
| 13 | Superior | > 6, > 6<br>> 6, > 6 | 2 | L4,<br>L5<br>L4,<br>L5 | dx.<br>dx. | None |
| 14 | Inferior<br>Inferior | > 6<br>> 6 | 2 | L5<br>L5 | sin.<br>sin. | Sensomotor deficit (L5) on the left |

## 5.2 Biocompatibility and performance of bioactive glass S53P4 putty compared to granules in rabbit model

### *5.2.1 Clinical and macroscopic follow-up*

Three female animals died prematurely before the scheduled necropsy. One of them died 13 days after the implantation of the test material, the other 29 days after the placement of the control implant, and the third 34 days after the placement of the control implant. Histopathological results for the animals living 29 and 34 days were reported as at four weeks. After macroscopic evaluation and microscopic analysis of the selected systemic and implantation site specimens, it was concluded that premature deaths were unrelated to treatment with either the test or control item. Altogether, there were no clinical signs of complications, e.g. cervical scabs, sores, hair loss, nodules or wounds.

Treatment-related effects on food consumption or body weight were observed with neither the test nor control animals. Furthermore, no treatment-related differences were recorded in haematological or clinical biochemistry parameters of the test or control animals. Occasionally, some statistically significant intergroup variations were detected, considered to primarily reflect the normal biological variation. All clinical and macroscopic findings were considered to be incidental, and commonly occur in rabbits of this strain and age under the experimental conditions as in this study.

### *5.2.2 Bone regeneration*

In both the BAG S53P4 putty test group and in the BAG S53P4 granule control group, generally a high cortical ossification along with a high integration of granules in the new bone were observed at four and eight weeks after implantation. Also, the volumes of the cortical defects were detected to be abundantly filled by the implants and the new bone, and the granules showed significant structural changes in both groups at both time points. All these findings were slightly more prominent eight weeks post-implantation when compared to four weeks post-implantation (Figure 6). The remaining volume of the defects consisted of stromal cell reaction localized mainly around implants, or connective tissue containing blood vessels and occasionally bone marrow cells. Considerable intramedullary ossification and stromal cell reaction were seen in both groups. However, both findings were slightly more advanced in the BAG S53P4

putty group when compared to the control group ($p = 0.001$ for intramedullary ossification and $p < 0.001$ for stromal cell reaction at eight weeks), indicating a slightly better formation of new bone in the medullary cavity (Figure 6). The spheres in the BAG S53P4 putty composition showed fewer structural changes and integration in the new bone than granules in the BAG S53P4 putty at four and eight weeks post-implantation, when they were mainly surrounded by fibrosis and inflammatory cell infiltrates of mainly round cells, as well as fibroblasts and fibrocytes. This stromal cell reaction is a normal and desired process in the formation of new bone (Wang et al. 2017).

In both groups, the destroyed periosteum grew back over the defect with variable degrees of fibrosis depending on the quantity of the periosteal implants present; the more implants were present, the more fibrosis was observed. At four weeks post-implantation, the degree of periosteal growth and fibrosis were slightly higher than at eight weeks post-implantation (Figure 6). High vascularization was observed in all sites of implantation.

### *5.2.3 Adverse effects*

Systemically in the soft tissues outside the implantation site, the microscopic examination of the selected specimens revealed from slight to moderate lymphoid atrophy in the spleen, higher degrees of lymphoid atrophy in the thymus, and one case of slight acute tubular necrosis in the kidneys. All of these disorders were considered to be secondary, relating to stress of the laboratory animals. Neither in the microscopic examinations of implantation site or selected systemic specimens, blood tests, specimens of urine, nor in clinical or macroscopic follow-up were cytotoxic cells or signs observed in the animals of either group. Thus, both the test and control items were considered to be biocompatible. No cartilage tissue was observed in any of the tibial bone samples examined.

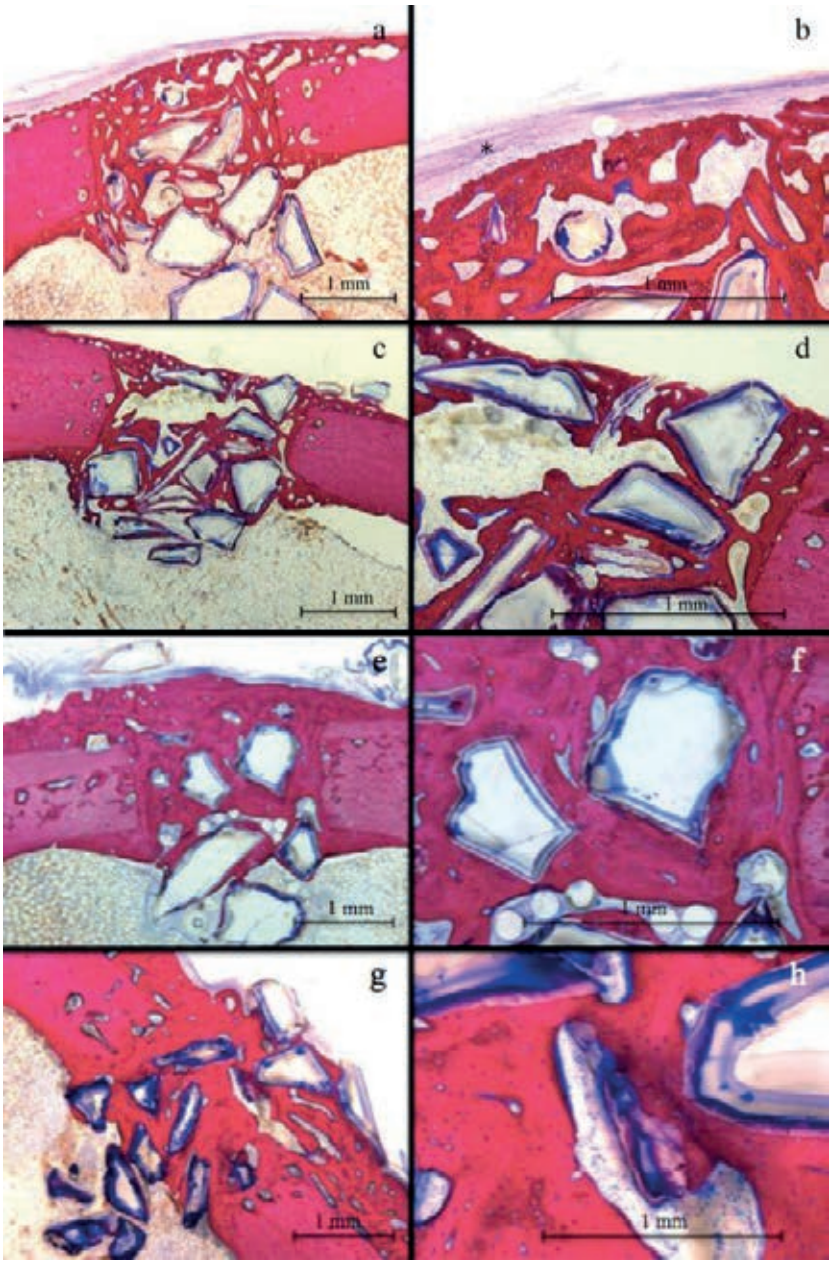


Figure 6 Histological examples of bone defects filled with the BAG S53P4 putty four (a, b) and eight (e, f) weeks post-implantation, or with the control BAG S53P4 granules four (c, d) and eight (g, h) weeks post-implantation (paragon stain, rabbit tibial bone). Four times magnification in a, c, e and g. Ten times magnification in b, d, f and h. Asterisk indicates periosteal growth and fibrosis. Scaled bars are 1 mm. (Modified from publication II.)

## 5.3 Bioactive glass S53P4 putty as bone graft expander in minimally invasive lumbosacral fusion

### *5.3.1 Resorption of bioactive glass S53P4 putty*

From routine static plain lumbar spine radiographs, the achieved interbody fusion could not be reliably estimated, but instead the resorption of the mixture of BAG S53P4 putty and autograft chips was graded. At three months postoperative, the above-mentioned mixture was still distinguishable in the fusion area in 58.3 % of the levels, whereas only in 8.3 % at twelve months, and in 5.3 % at 24 months postoperative compared to immediate postoperative radiographs. In contrast, the mixture was not distinguishable in 4.2 % of the levels at three months, in 37.5 % at twelve months, and in 47.4 % at 24 months postoperative (Table 6). The resorption was significantly more progressed in radiographs at twelve months compared with those at three months post-implantation ($p < 0.001$), but not in radiographs at 24 months compared with those at twelve months post-implantation ($p = 0.135$).

### *5.3.2 Interbody and posterolateral fusion rates*

The patients were further investigated with lumbar CT with or without MRI scans, if indicated, based on postoperative symptoms or clinical monitoring at the follow-up visits. Altogether, ten CT scans were done for eight patients at 1–18 months postoperative (mean: 10.3 months, SD: 6.0 months). Bridging bone across the intervertebral space was observed in all CT scans. According to bridging bone criteria, five of the nine investigated levels were graded as definitely fused and four levels as probably fused. The scans showing grade II (probably fused) were carried out at 1–18 months postoperative. One patient was observed to have a cage dislocation of 2–3 mm posteriorly in a static plain radiograph in the L5/S1 level at three months postoperative, and lucency around a sacral screw and a breakage of the other sacral screw in CT scan at nine months postoperative. Fifteen patients (75.0 %) had posterolateral bone graft mixture unilaterally on the transverse processes and one patient bilaterally. However, only one of the seventeen levels showed Bridwell grade 1 fusion (fused with remodelling and trabeculae present), whereas the remaining sixteen levels were graded as Bridwell grade 4 (fusion absent with collapse/resorption of graft) in CTs and static plain radiographs at twelve months postoperative.

Table 6 Radiological and clinical outcome with BAG S53P4 putty as bone graft expander in minimally invasive lumbosacral fusion surgery. (Modified from manuscript III.)

| | |
|---|---|
| Radiological follow-up time, mean (SD) (months) | 21.1 (6.3) |
| Resorption grade at 3 months, n (%) | |
| 1 | 14 (58.3) |
| 2 | 9 (37.5) |
| 3 | 1 (4.2) |
| Resorption grade at 12 months, n (%) | |
| 1 | 2 (8.3) |
| 2 | 13 (54.2) |
| 3 | 9 (37.5) |
| Resorption grade at 24 months, n (%) | |
| 1 | 1 (5.3) |
| 2 | 9 (47.4) |
| 3 | 9 (47.4) |
| Clinical follow-up time, mean (SD) (months) | 19.0 (7.6) |
| Low back pain, n (%) | |
| Relief | 14 (70.0) |
| New | 0 (0.0) |
| Radicular pain, n (%) | |
| Relief | 14 (70.0) |
| New | 2 (10.0) |
| Motor deficit, n (%) | |
| Relief | 5 (25.0) |
| New | 1 (5.0) |
| Paresthesia, n (%) | |
| Relief | 4 (20.0) |
| New | 2 (10.0) |
| Instability symptoms, n (%) | |
| Relief | 8 (40.0) |
| New | 0 (0.0) |
| Odom's criteria, n (%) | |
| Excellent | 8 (40.0) |
| Good | 5 (25.0) |
| Fair | 3 (15.0) |
| Poor | 4 (20.0) |

### *5.3.3 Subsidence*

One patient had an early intervertebral cage subsidence of the upper endplate and vertebral bone of 6 mm already in the intraoperative 3D flat panel scan. This subsidence remained unchanged until the last routine follow-up radiograph at ten months postoperative. The mean disc height preoperatively was 6.3 mm (SD: 1.7 mm) and postoperatively 7.9 mm (SD: 1.2 mm), while the median increase in disc height was 1.0 mm postoperatively compared with the height preoperatively ($p < 0.001$).

### *5.3.4 Clinical outcome*

Postoperatively, two patients presented new radicular pain, one new motor deficit and two new paresthesiae. In contrast, fourteen patients expressed relief of low back pain, fourteen of radicular pain, eight of instability symptoms, five of motor deficit, and four of paresthesia. The clinical outcome of the patients was described at the last clinical follow-up visit according to Odom's criteria as excellent or good in 65.0 % of the patients and poor in 20.0 % of the patients (Table 6).

# 6 DISCUSSION

## 6.1 Pedicle screw placement in degenerative lumbar spine

In this study, the average pedicle perforation rate of 14.3 % is well within the widely reported range of 1.2–41.0 % in the literature (Table 3) (Schulze et al. 1998, Koktekir et al. 2014). The mean proportion of 70.3 % of either medially or inferiorly breached pedicles in our study is also consistent with earlier studies, with the rate of either medial or inferior breaches being between 26.7 and 88.9 % when discarding the studies with postoperative pedicle screw position assessment based only on radiographs (Lonstein et al. 1999, Oh et al. 2013, Nevzati et al. 2014). The detection of medially breached pedicles has been proved to be 8–10 times more precise on CT scans compared to plain radiographs (Weinstein et al. 1988, Farber et al. 1995). The incidence of so-called high risk pedicle breaches of ≥ 4 mm of 3.4 % in our study is well within the range of 0–9.0 % reported earlier, when excluding the studies where pedicle screw is graded only as in or out, or the perforation as ≤ 3 mm (Luther et al. 2015). The reason for the statistically significant screw breach rate medially and inferiorly more on the left side is probably due to the right-hand dominance of the operative surgeon.

Twenty-four patients (16.3 % of all patients) in our study had new neurological symptoms corresponding to the pedicle perforation site, and nine patients of this cohort had a pedicle perforation of ≥ 4 mm (37.5 % of patients with new neurological symptoms). Altogether 89.2 % of the patients with neurological symptoms corresponding to screw breach site had an evaluated screw-breach either medially or inferiorly. Nine of ten patients with pedicle perforation of at least 4 mm medially or inferiorly had new neurological symptoms corresponding to the breach. These results indicate that the direction of the breach may be more important than the absolute magnitude of deviation in causing postoperative neurological symptoms. No early revision in our data was performed for screw misplacement.

In a recent multi-centric retrospective study of 401 patients with 1467 lumbosacral pedicle screws, 25.3 % of the screws breached the pedicle and 63.3 % of the breaches were inferomedial, when the directions of the breaches were divided into inferomedial, lateral or superior in CT-based postoperative assessment (Yu et al. 2017). The authors reported three postoperative transient nerve root injuries and nine CSF leakages, but no early revisions were needed. When 17 different neurosurgeons at all levels of experience performed the thoracolum-

bosacral pedicle screw insertions, 20.0 % of 1236 screws were identified as perforating the pedicle in postoperative CT scans; 3.2 % of the screws breached the pedicle by at least 4 mm at L1-S1 levels (Nevzati et al. 2014). Sixteen patients (5.9 %) had new radicular pain and/or sensorimotor deficits. Of the symptomatic screws, 88.9 % breached the pedicle either medially or inferiorly. In a large comparison study of CT-navigation and fluoroscopy-guidance, 29.5 % of 1394 lumbosacral screws were detected to breach the pedicle wall in the fluoroscopy-supported group; 1.8 % of the screws breached the pedicles by 4 mm or more (Waschke et al. 2013). Of the breaches, 51.8 % were graded as perforating medially by at least 2 mm. Nine nerve root lesions (four affecting L5) causing motor weakness, and two patients with myelopathy symptoms due to screw perforations in 2.2 % of the operations in the thoracolumbosacral spine were detected. When pedicle screw insertion in the thoracolumbar spine was compared between two groups, in which the screws were inserted either with the assistance of lateral fluoroscopy only (group 1) or with the assistance of lateral and AP fluoroscopy (group 2), 1.2 % of the screws were more than 25 % outside the pedicle in the latter group, while 25.0 % of those to the medial direction (Koktekir et al. 2014). None in the second group had any neurological symptoms. The authors concluded that the use of intraoperative AP fluoroscopy significantly decreases the risk of screw misplacement. When lateral radiography was used to confirm the screw placement intraoperatively, and when intraoperative AP radiographs were used only occasionally in the thoracolumbar spine, 1.7 % of 6816 screws breached the pedicle by more than 25 % of the screw diameter, and 33.9 % of these medially (Parker et al. 2011). Only 0.3 % of the patients had new neurological symptoms postoperatively due to breached screws, which all breached medially.

As the misplaced screws reduce the stability of the construct and may cause later screw loosening, the accuracy of pedicle screw placement is not only a question of nerve root damage (Laine et al. 1997). In this study, symptomatic cases with assessed breached pedicle screws have been treated conservatively based on the decision of the operative surgeon. Despite the spread of computer-assisted techniques in the pedicle screw insertion, screw application based on anatomical landmarks supported by radiography is still relatively commonly used. This study provides a single, very experienced spine surgeon series on degenerative indications, where pedicle breach was assessed and graded in an accurate way, including a long-term follow-up from the patient records for clinical symptoms related to the instrumented fusion.

## 6.2 In vivo biocompatibility and performance of bioactive glass S53P4 putty

This study compared the use of the novel BAG S53P4 putty with BAG S53P4 granules for filling bony non-CSDs in the tibial bones of twenty-eight rabbits to find out whether the synthetic binder has any effects on the performance of the granules and formation of new bone. Our results revealed ossification and integration of both the BAG S53P4 putty and the granules within the new bone in the cortex and medullar. Both the test and the control samples were considered to be biocompatible, and showed high new bone formation along with high vascularization and periosteal growth. With the BAG S53P4 putty, no indication of possible disturbed bone formation by the PEG-glycerol binder was seen. This is in line with the studies carried out using the closest comparable device, NovaBone putty® consisting of 69 weight-% BAG 45S5 granules mixed with spherical granules (sizes 32–90 μm and 90–710 μm, respectively) and 31 weight-% binder (Kobayashi et al. 2010, Wang et al. 2011).

Actually, in our study, the bioactive glass granules in the BAG S53P4 putty showed a slightly higher intramedullary ossification than the controls, but no difference in the cortical ossification was seen. When using a sheep vertebral CSD model, similar findings at six and twelve weeks post-implantation with NovaBone putty® have been shown, revealing a greater bone content in the putty group than in the granule group (Wang et al. 2011). A possible explanation for the increased bone formation with the putty may be that the putty matrix separates the granules, providing a better spatial distribution and allowing more new bone to grow between them than the tightly packed granules (Wang et al. 2011). Also, the pH environment created by the putty may be more suitable for bone ingrowth than pH produced by tightly packed granules (Jones 2013). As the granules in the putty are embedded in a water-soluble synthetic binder matrix, they are not immediately exposed to the aqueous environment, and there is thus a delay in the surface reactions. A sequential reaction cascade with granules originates on the surface of the putty mass in the defect. The granules in the middle of the putty mass react after a certain delay subsequent to the extracellular fluids in living tissue reaching the middle.

Further, an earlier study also using the sheep vertebral CSD model to compare NovaBone Putty® with or without autograft, and NovaBone BAG granules did not show any significant difference in new bone formation either among the graft materials or between the graft materials and the empty defects at six and twelve weeks after implantation (Kobayashi et al. 2010). All granule formulations were shown to be associated with an inflammatory reaction at both six and

twelve weeks post-implantation. When utilizing a rabbit cranial CSD model, the OsteoSelect DBM putty was associated with less inflammation and fibrous tissue in the defect, and significantly more bone formation in the histomorphometric analysis than the synthetic NovaBone Putty® at 43 and 91 days post-implantation (Schallenberger et al. 2014). In μCT and histomorphometric comparison of two synthetic bone graft products using a rabbit PLF model, Signafuse® Bioactive Bone Graft Putty, consisting of BAG 45S5 and biphasic HA/ß-TCP granules, showed greater new bone formation than the Actifuse® ABX sculptable bone graft substitute, consisting of 0.8 % silicate-substituted HA, at six weeks post-implantation, but no further differences were detected at twelve weeks (Fredericks et al. 2016). However, histological fusion scores were greater in the Signafuse group at both six and twelve weeks post-implantation, indicating higher structural remodelling and a tendency towards a complete bridging fusion bed compared to the Actifuse group.

Despite the observation that the BAG granules pack into a defect easily and stay in place, even when the site is bleeding in the periodontal treatment model, several studies report difficulties in keeping the bioactive glass granules within the experimental defects (Wilson et al. 1992, Amato et al. 2003, Moreira-Gonzalez et al. 2005, Kobayashi et al. 2010). Once the granules migrate, they start to degrade in the soft tissue and are associated with an intense inflammatory reaction (Moreira-Gonzalez et al. 2005). Also, many of the BAG granules have been suggested to contain cracks and a hollow centre, into which cells can migrate. These cavities have been shown to associate with acute inflammation (Kobayashi et al. 2010). Further, varied degrees of inflammation, from acute to chronic, are associated with collection of either lymphocytes and plasma cells, or macrophages and giant cells (Moreira-Gonzalez et al. 2005, Kobayashi et al. 2010). In this study, neither signs of inflammation nor migration of the granules were observed. Due to its physical properties, unlike the granules, the putty can be shaped so that the bone defect can be filled easily with little residual implant migrating into the undesirable areas (Wang et al. 2011). Besides, the increase in early bone deposition rate may allow subjects to start functional recovery training as early as possible (Wang et al. 2011).

## 6.3 Use of bioactive glass S53P4 putty as bone graft expander in minimally invasive lumbosacral interbody fusion

Assuming that patients not fused would be symptomatic within twelve months postoperatively, the interbody fusion rate of this study was determined to be 95.8

% with the mixture of BAG S53P4 putty and autograft by CT-scan assessment. Although several studies have shown a lack of correlation between radiological fusion rate and clinical success, many other studies have observed that the presence of radiological pseudoarthrosis correlates with poorer clinical outcome (Herkowitz et al. 1991, France et al. 1999, Fritzell et al. 2002, Santos et al. 2003, Kornblum et al. 2004, Lamberg et al. 2005, Resnick et al. 2005, Champain et al. 2007, Djurasovic et al. 2011). However, the previous studies may be confusing in rating the clinical outcome, and inaccurate in assessing the radiological fusion rate by plain radiographs. In a recent study, which evaluated the fusion rate based on CT scans, solid fusion was shown to contribute to clinical outcome (Djurasovic et al. 2011). On the other hand, a reliable radiological method to distinguish ceramics and newly formed bone is still under development (Heino 2018, and N. C. Lindfors, personal communication, April 25, 2018). In our study, fifteen patients completed a two-year follow-up without hardware failure. Two patients with new postoperative radicular pain, one patient with new L5 motor weakness, and two patients with new paresthesia were further investigated with lumbar spine CT with or without MRI. One patient suffering from new radicular pain had a clear hardware failure. The patient with new motor weakness had a new disc herniation in the lower operated level, but the symptoms were relieved with conservative treatment. In another patient, a new paresthesia, due to an adjacent level disc herniation was relieved with conservative treatment. In the remaining two patients, no explanation for radicular pain and paresthesia was found. No postoperative infections were detected.

When using autograft or allograft with or without rhBMP-2, a systematic review suggested 83.4–100 % fusion rates for MI-TLIF in the degenerative spine (Chaudhary et al. 2011). In another systematic review of 408 patients, an average interbody bridging of 94.7 % is presented for MI-TLIF with autograft or allograft with or without rhBMP-2 (Bevevino et al. 2014). Interbody bridging was observed in 88.0 % of the levels over twelve months and in 95.0 % of the levels over 24 months, when using a variety of different graft materials (autograft, allograft cellular bone matrix, BMA, rhBMP-2, corticocancellous chips, DBM) alone or in combination, in the MI-TLIFs of 26 patients (Isaacs et al. 2016). In a recent meta-analysis of 1533 patients, interbody bridging ranging between 91.8 and 99.1 % was detected using combinations of autograft with or without allograft and rhBMP, and interbody bridging rates of 96.6 % and 92.5 % were detected with and without rhBMP, respectively (Parajón et al. 2017). The lowest interbody bridging rate was seen with isolated use of local autograft (91.8 %), and the highest by using local autograft with bone expander and rhBMP (99.1 %). Fur-

thermore, the highest interbody bridging rate without the use of BMP was achieved with local autograft and bone expander (93.1 %) (Parajón et al. 2017).

When the achieved fusion rates were compared in MI-TLIFs between the combinations of local autograft and silicate-HA ceramic bone graft expander (ActifuseTM), and local autograft and rhBMP-2, a radiological fusion of 65 % in the Actifuse cohort and 92 % in the rhBMP-2 cohort was established in a prospective, randomized and controlled study of a total of 52 patients (Nandyala et al. 2014). Only in 26.7 % of the levels was solid fusion, in 34.1 % indeterminate and in 38.6 % inadequate fusion assessed in PLIFs filled with β-TCP and BMA based on CT scans at twelve months postoperative, in a prospective study of 34 patients (Thaler et al. 2013). In a prospective study of 76 patients, using β-TCP with a resorbable polymer (ChronOSTM Strip) together with BMA and local autograft in PLF with interbody support, interbody fusion rates of 54.1 % and 71.2 % were achieved in CTs at twelve and 24 months postoperative, respectively (Kanter et al. 2016). Interbody fusion rates of 84.6 % and 92.3 % were estimated for a type 1 collagen/HA matrix (Healos®) with BMA, and autograft, respectively, in PLIFs of fifty patients with dynamic and static plain radiographs at 24 months postoperative (Neen et al. 2006). Furthermore, (1) HA bone chip and local autograft, (2) iliac crest autograft and local autograft, and (3) local autograft groups were shown to have 91.7 %, 92.9 %, and 94.6 % fusion rates, respectively, in TLIFs of 130 patients and 165 operated levels evaluated by static plain radiographs at twelve months (Kim et al. 2012). A mixture of local autograft and bioactive apatite-wollastonite granules containing glass ceramic yielded solid fusion in 92.0 % of TLIF levels of 25 patients in static and dynamic plain radiographs at six months postoperative (Hashimoto et al. 2002).

Defined as the sinking of an interbody device into a vertebral endplate of at least 2–3 mm, subsidence may defeat the purpose of the interbody fusion, resulting in a loss of disc height, partial loss of ligamentous stability, the return of foraminal stenosis and ensuing nerve root stenosis (Tokuhashi et al. 2009, Le et al. 2012). Particularly at the L4/L5 and L5/S1 levels, subsidence may also result in the loss of lordotic correction with consequent sagittal imbalance (Malham et al. 2017). In our study, one early operative subsidence was detected (4.2 %). In a prior MI-TLIF study using a PEEK cage filled with autograft, the rates of cage subsidence of > 2 mm and of > 4 mm were 14.8 % and 6.6 %, respectively, at the last follow-up at 24–45 months postoperative, and the subsidence occurred on average at 7.2 months postoperative (SD: 8.5 months, range: 1–25 months) (Kim et al. 2013). In another study on TLIF, a subsidence of ≥ 10 % was detected in 52.9 % with the allograft spacer and adjuvant rhBMP-2, and in 12 % with the allograft/DBM (Vaidya et al. 2007). In our study, only one of the seventeen lev-

els with the posterolateral mixture of BAG S53P4 and autograft led to formation of solid bony PLF; this may be due to shortage of stress for remodelling posterolateral bone because of the well-supporting and load-bearing framework of the interbody cage, and later interbody fusion (Grabowski et al. 2013).

When the amount of local autograft is limited in quantity as is the case with mini-invasive approaches and revisions, a bone graft expander is needed to aid fusion. In the literature, the rate of interbody fusion ranges between 83.4 and 100 % with either autograft or allograft with or without rhBMP-2, and between 26.7 and 92.0 % with ceramics as a bone graft expander together with other bone grafts, substitutes or enhancers. Our interbody fusion rate of 95.8 % with BAG S53P4 putty as bone graft expander together with autograft is close, but seems not to be inferior compared to the earlier results with ceramics that include several confusing factors, e.g. no autograft or allograft was used together with ceramics (Thaler et al. 2013). As listed in section 2.1.4.3, many variables affect the interbody fusion rate, and hence further comparison studies are needed to confirm the interbody fusion results of this study. However, compared to the earlier studies, BAG S53P4 putty seems not to increase the subsidence of an interbody implant.

## 6.4 Strengths and limitations of the study

There are only few studies on the accuracy of pedicle screw position in lumbar spine with larger data than presented here (Lonstein et al. 1999, Parker et al. 2011, Waschke et al. 2013, Koktekir et al. 2014, Nevzati et al. 2014, Yu et al. 2017), and only one with a single surgeon series, like in this study (Koktekir et al. 2014). The treatment indications also varied among the studies, while our study concentrated on degenerative indications (Parker et al. 2011, Waschke et al. 2013, Yu et al. 2017). The follow-up time usually consisted only of the immediate postoperative period in the hospital, and mostly until the first follow-up admission except for one study with other shortcomings (Lonstein et al. 1999). The most important limitations in our study are its retrospective nature and the lack of a comparison group for pedicle screw positioning with another technique, e.g. spinal navigation. Also, no routinely appointed admission was arranged after the first year follow-up. Additionally, the present study is the experience of a single centre and a single surgeon, and is hence not generalizable. A further limitation is the lack of analysis of potential risk factors such as long operation time, scoliosis, former spinal surgeries with, e.g. scarring and the loss of anatomical landmarks, and low bone density. Moreover, pain, disability and quality of life

determinations, such as VAS, ODI and SF questionnaires have not been routinely used.

Our prospective study comparing the use of novel BAG S53P4 putty to BAG S53P4 granules in terms of biocompatibility and performance is the first preclinical study performed with BAG S53P4 putty. The study was carried out in well-controlled conditions with appropriate laboratory animal monitoring for clinical signs or symptoms, and with daily food consumption and body weight controls. Additionally, blood and urine were sampled for extensive clinical laboratory investigations, and selected systemic specimens were weighed, and implantation site and systemic specimens histologically assessed after the termination of the animals. The histological assessment of the implant site is the most precise method to achieve information about tissue characteristics, along with the evaluation of bone regeneration. The study included a control group, and the follow-up time was adequate in terms of histological findings. Also, the results of the study were in line with the corresponding earlier study of the closest comparable device (Wang et al. 2011). The most important limitation of the study is that the used cavital monocortical defect is not a CSD. Consequently, the defect could have been filled with new bone even without any implant, and hence no conclusions on the osteoconductive or osteostimulative characters of the implant can be drawn. Also, no control group of empty defects was used. The study also lacks quantitative histomorphometric analysis of the amount of formed bone.

Our study of the use of BAG S53P4 putty as bone graft expander in lumbosacral MI-TLIF operations is the first clinical study carried out with BAG S53P4 putty. BAG S53P4 putty was implanted in an extensively studied application of lumbosacral interbody fusion and mixed together with autograft. The main results of the study regarding the interbody fusion rate and subsidence are close to or in line with the earlier reported results with other ceramics as bone graft expanders. The major limitations of the study, in addition to its retrospective nature, are the small sample size; the lack of a reliable radiological method to distinguish ceramics and newly formed bone; the lack of routine quantitative pain, disability and quality of life determinations; and the lack of a control group. Based on the small sample size, the study may not determine the real incidence of the pseudoarthrosis. Although the CT scans would have been more reliable than plain radiographs in assessing fusion, their use is not allowed for non-symptomatic patients based on the principles of justification and optimization of ionizing radiation associated with CT (Santos et al. 2003, Carreon et al. 2007b, Selby et al. 2012).

## 6.5 Future prospects in lumbosacral fusion surgery and research

In recent decades and years, lumbosacral fusion surgery has undergone a vigorous progression in several sectors including more profound understanding of spine biomechanics in operative design; development of minimally invasive approaches for less approach-related morbidity; utilization of modern facilities, particularly spinal navigation and intraoperative imaging for better accuracy, and development of novel biomaterials, such as ceramics to enhance fusion. However, there is still one shortcoming in our knowledge, i.e. in selecting the patients for operation who would benefit from lumbosacral fusion. No definitive combination of signs, symptoms and radiological findings could have been evolved for the patient selection. As the pain is a common symptom, aids to assess chronic pain and the pain affect component play a crucial role in the treatment decision for successful outcome.

So far, of the existing navigation techniques, the intraoperative CT spinal navigation has been shown to be superior in the accuracy of pedicle screw placement. On the other hand, the interbody fusion methods have been proved to achieve higher fusion rates compared to posterolateral fusion, based on biomechanical factors. Nevertheless, the robotic surgery in lumbosacral fusion applications is still under strong development, and may provide advantages of, e.g. excellent 3D visualization, reduction in approach-related morbidity, enhanced dexterity, and reduction of radiation. Also, a novel midline procedure with a cortical bone trajectory for lumbosacral pedicle screws would provide even less approach-related morbidity, as well as an increase in the pullout strength of the pedicle screws compared with the traditional approach (Santoni et al. 2009, Su et al. 2009). The rapid progression of different lumbosacral fusion sectors warrants research in the form of a long-term prospective study with appropriate pain, disability and quality of life determinations; and imaging studies including the assessment of the adjacent segment changes with variables of operative design, approach, use of modern facilities and biomaterials.

In the sector of bioactive glass ceramics, the clinical use of bioactive glasses has been proved safe, and they have been shown to be a viable option as a bone graft expander in the lumbosacral fusion surgery. New manufacturing methods enable the production of glass structures which mimic porous bone or which have large channels, and thus a large surface area, but greater compressive strengths than porous bone (Jones 2013). Also, inorganic-organic hybrid bioactive materials may mimic bone nanostructure, and hence have tailorable mechanical properties and degradation rates. These new bioactive materials may be optimized for their respective purpose. With the delivery properties of drugs or oth-

er molecules, bioactive glasses can also be utilized to enhance fusion locally. First, a prospective and randomized clinical study with a comparison group, e.g. of autologous bone, is needed to further analyse and confirm particularly the interbody fusion, but also the subsidence results of our clinical study on bioactive glass S53P4 putty as bone graft expander together with autologous bone in minimally invasive lumbosacral interbody fusion. This could be done in connection with the development of a precise 3D imaging method able to distinguish ceramics from newly formed bone that is ongoing at the University of Helsinki.

# 7 CONCLUSIONS

1) (I) The total pedicle perforation rate of 14.3 % in our study was consistent with the results of earlier studies with multiple surgeons (Table 3). Even in very experienced hands, the accuracy of pedicle screw placement seems not to meet the present demands, since in our study 3.4 % of the screws were judged to be 4 mm or more, and 1.9 % of the screws 6 mm or more out of pedicle. In order to meet the increasing demands when treating the degenerative lumbosacral spine, the routine utilization of spinal navigation and intraoperative imaging will most probably increase the pedicle screw position accuracy.

2) (II) In the preclinical study with the novel BAG S53P4 putty, no indication of possible disturbed bone formation by the PEG-glycerol binder was observed. The BAG S53P4 putty showed even a slightly higher intramedullary ossification than the controls, and no difference in the cortical ossification was found between the test and control items. Neither in the microscopic examinations of implantation site or selected systemic specimens, blood tests, specimens of urine, nor in clinical or macroscopic follow-up were cytotoxic cells or signs observed in the animals of the test or control groups. Thus, the bioactive glass S53P4 putty can be considered to be biocompatible and non-toxic.

3) (III) When the amount of local autograft is limited in quantity, such as in clinical minimally invasive lumbosacral interbody fusion surgery, a synthetic bone graft expander is required in order to avoid the drawbacks associated with harvesting of autologous bone graft, and with the use of allogenous bone graft. In spite of the limitations of our study with regard to small sample size and shortcomings in the reliability of the radiological method, our results of an interbody fusion rate of 95.8 % with a mixture of the BAG S53P4 putty and autologous bone suggest that the bioactive glass S53P4 putty provides results comparable to those of the earlier studied ceramics as bone graft expanders together with autologous bone in minimally invasive lumbosacral interbody fusion surgery.

4) (III) Compared to earlier reported subsidence rates with TLIF of 6.6 % over 2 mm with autograft, of 52.9 % with least 10 % of the implant height with allograft and rhBMP-2, and 12 % with least 10 % of the implant height with allograft/DBM, our study detected only one early operative subsidence with the rate of 4.2 %. Thus, according to our results, the bioactive glass S53P4 putty

seems not to increase the subsidence of an intervertebral cage in clinical minimally invasive lumbosacral interbody fusion surgery.

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